DEMOGRAPHIC PROFILE AND MANAGEMENT STRATEGIES OF TREATMENT RESISTANT SCHIZOPHRENIA AND TREATMENT RESISTANT DEPRESSION IN A TERTIARY CARE REFERRAL HOSPITAL

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IMMANUEL JEBASTIN Mpharm

SUBMITTED BY

SHAYANA.S

REGISTER NUMBER: 261540716

DEPARTMENT OF PHARMACY PRACTICE

PADMAVATHI COLLEGE OF PHARMACY

DHARMAPURI-635205

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Dr. V. MAITHILI,M.Pharm,Ph.D,
Principal,
Padmavathi College Of Pharmacy
Periyanahalli, Dharmapuri, Tamilnadu.

CERTIFICATE

This is to certify that this dissertation work entitled"**DEMOGRAPHIC PROFILE AND MANAGEMENT STRATEGIES OF TREATMENT RESISTANT SCHIZOPHRENIA AND TREATMENT RESISTANT DEPRESSION IN A TERTIARY CARE REFERRAL HOSPITAL "**constitute the original work carried out by **SHAYANA.S** Reg no:**261540716,** under the guidance and supervision of **IMMANUEL JEBASTIN, M.pharm,** department of pharmacy practice,Padmavathi college of pharmacy and Research institute,Periyanahalli,Dharmapuri,Tamilnadu-635205

Principal

Date: **Dr.V. MAITHILI,M.pharm,Ph.D**

Place: DHARMAPURI

Prof.Dr.R.ANANDAN, M.Pharm, Ph.D
HOD,Department of Pharmacy Practice,
Padmavathi College Of Pharmacy
Periyanahalli, Dharmapuri, Tamilnadu.

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Prof.Dr.R.ANANDAN ,M.Pharm,Ph.D
Department of pharmacy practice

Date:
Place:Dharmapuri

IMMANUEL JEBASTIN. M.Pharm,

Department of Pharmacy practice,

Padmavathi College Of Pharmacy

Periyanahalli, Dharmapuri, Tamilnadu.

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GUIDE

IMMANUEL JEBASTIN. M.Pharm,

Date: Department of pharmacy practice

Place:Dharmapuri

EVALUATION CERTIFICATE

This is to certify that dissertation entitled **"DEMOGRAPHIC PROFILE AND MANAGEMENT STRATEGIES OF TREATMENT RESISTANT SCHIZOPHRENIA AND TREATMENT RESISTANT DEPRESSION IN A TERTIARY CARE REFERRAL HOSPITAL"**constitute the original work carried out by **SHAYANA.S** Reg no:**261540716,** under the guidance and supervision of **IMMANUEL JEBASTIN. M.Pharm,** department of pharmacy practice,Padmavathi college of pharmacy and Research institute,Periyanahalli,Dharmapuri,Tamilnadu-635205 has been evaluated on

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Evaluators

1.

DEDICATED TO ALMIGHTY, OUR BELOVED PARENTS, TEACHERS AND FRIENDS

ABSTRACT

ABSTRACT

Treatment resistance is an emerging issue faced by physicians worldwide. The incidence of treatment resistance in schizophrenia is about 20%.Factors that may contribute to it include non-adherence to treatment, comorbid conditions and medication side effects. Clozapine, augmentation of clozapine with benzamides (sulpiride, amisulpride), antiepileptics (lamotrigine) and atypical antipsychotics shows some success in management of TRS. In extreme treatment resistance, a strategy is recommended that combines the proven best drug for the particular patient and psychosocial treatments. Treatment resistant depression is a severely disabling disorder which affects about 30-46% of patients with major depressive disorder. Although there are no proven treatment options, therapeutic strategies which include optimization of medications, a combination or switching of anti-depressants and an augmentation with non-antidepressants, psychosocial and cultural therapies and somatic therapies including ECT etc. are used.

The current study was aimed at evaluating the demographic profile and management of treatment resistant schizophrenia and treatment resistant depression in psychiatric department of a tertiary care super-specialty hospital. The design of the study was prospective observational and a total of 52 subjects were enrolled in the study of which 25 subjects were diagnosed with TRS and 27 were diagnosed with TRD. Treatment resistant cases in the hospital setting were identified by using PANSS and MADRS scales. We evaluate the treatment provided for those patients and monitor for improvement of conditions. Even though many treatment options are available, a well-defined management guideline is not yet established. So we hope this study may contribute something new to the health care professionals, thereby helps improve patient care. From the evaluation of the demographic profile, it concluded that the gender doesn't have much influence on the occurrence of TRS. But in cases of TRD, females had predominance over males. Furthermore family history had a strong correlation with the occurrence of both TRD and TRS.

Clozapine is used as a gold standard in treatment of TRS. Augmentation of clozapine with other antipsychotics in different doses has shown clinical improvement in patients. Sertraline, Venlafaxine and Sodium valproate combination was majorly used in the treatment of TRD patients. Among them, Venlafaxine was used commonly in TRD.

Adverse drug reactions are common with the use of antipsychotic drugs. There for this study monitor the occurrence of major adverse drug reactions in patients with TRS and TRD. In this study the major ADRs shown by TRS patients include weight gain, constipation, diabetes mellitus, extra pyramidal symptoms, sexual dysfunction and tachycardia and those of TRD patients include weight changes, GI problems and sexual dysfunction.

The study concluded that in TRS, this specific population unresponsive to previous treatment, a combination of clozapine with aripiprazole, as well as other augmentation strategies for clozapine, seen worthy of further exploration. It also concluded that TRD may benefit from treatment with a more potent anti-depressant from the tricyclic anti-depressant class or selective serotonin reuptake inhibitor or using antipsychotic medication or selective nor epinephrine reuptake inhibitor or mood stabilizing medication such as lithium may hold the key to their recovery.

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INTRODUCTION

1. INTRODUCTION

Mental health (psychiatric or psychological) disorders involve disturbances in thinking, emotion and/or behaviour. Small disturbances in these aspects of life are common, but when such disturbances distress the person greatly and/or interfere with daily life, they are considered mental illness or a mental health disorder. The effect of mental illness may be long lasting or temporary. These disorders are caused by complex interactions between physical, psychological, social, cultural and hereditary influences. The most common mental disorders are obsessive compulsive disorder, posttraumatic stress disorder, anxiety, major depressive disorder, schizophrenia etc [1].

Depression is the major cause of morbidity worldwide among mental disorders [2]. Of all the patients who are taking treatment for depression, approximately 55% of patients meet the criteria for treatment resistance; that is those patients failed at least 6 week trial of two or more classes of antidepressants. The treatment resistance occurring along the continuing ranging from partial response to complete refractioneries [3].

Treatment-resistant depression, a complex clinical problem caused by multiple risk factors, is targeted by integrated therapeutic strategies, which include optimization of medications, a combination of antidepressants, switching of antidepressants, and augmentation with non-antidepressants, psychosocial and cultural therapies, and somatic therapies including electroconvulsive therapy, repetitive transcranial magnetic stimulation, magnetic seizure therapy, deep brain stimulation, transcranial direct current stimulation, and vagus nerve stimulation [3].

Schizophrenia, another commonly occurring mental illness, which is a chronic thought disorder in which characteristic psychiatric symptoms are seen during the acute phase of illness with partial or full resolution of symptoms between psychiatric episodes coupled with deterioration from the previous level of social or occupational functioning [4]. The impact of schizophrenia tends to be highest in Oceania, the Middle East and East Africa, while the nations of Australia, Japan, US and most Europe typically have low impact. A schizophrenic patient can be termed as resistant to treatment only after an inadequate response to trial of any two second generation antipsychotics or one first

generation and one second generation antipsychotics for duration of 4 to 10 weeks [5].The treatment resistance is as high as 15% even in first episode of schizophrenic patient. It is one of the most important clinical challenges in the pharmacological management of schizophrenia. Therefore the evaluation of the therapeutic options in case of treatment resistance is highly clinically relevant [6]. Treatment of TRS includes management with clozapine, atypical antipsychotics (risperidone, olanzapine, quetiapine, and amisulpiride), augmentation with antidepressants (fluoxetine, paroxetine, and fluvoxamine), mood stabilizers (valproate, carbamazepine, lamotrigine). Also electro convulsive therapy (ECT) has been used in combination with clozapine and has been found to be safe and clinically beneficial [7].

1.1 SIGNS AND SYMPTOMS

1.1.1 DEPRESSION

Five or more of the following symptoms present nearly every day for 2 weeks.

- Depressed mood most of every days.
- Marked decreased interest or pleasure in most all activities (anhedonia).
- Appetite or weight change (5% body weight in 1 month).
- Insomnia or hypersomnia.
- Psychomotor agitation or retardation.
- Fatigue or loss of energy.
- Worthlessness, excessive guilt.
- Decreased ability to think or concentrate indecisiveness.
- Recurrent thoughts of death, suicidal ideation or attempt [2].

1.1.2 SCHIZOPHRENIA

Either at least one of the syndromes, symptoms and signs listed below under (1), or at least two of the symptoms and signs listed under (2), should be present for most of the time during an episode of psychotic illness lasting for at least one month (or at some time during most of the days).

(1) At least one of the following:

a) Thought echo, thought insertion or withdrawal, or thought broadcasting.

b) Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception.
c) Hallucinatory voices giving a running commentary on the patient's behaviour, or discussing him between themselves, or other types of hallucinatory voices coming from some part of the body.
d) Persistent delusions of other kinds that is culturally inappropriate and completely impossible (e.g. being able to control the weather, or being in communication with aliens from another world).

(2) or at least two of the following:

a) Persistent hallucinations in any modality, when occurring every day for at least one month, when accompanied by delusions (which may be fleeting or half-formed) without clear affective content, or when accompanied by persistent over-valued ideas.
b) Neologisms, breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech.
c) Catatonic behaviour, such as excitement, posturing or waxy flexibility, negativism, mutism and stupor.
d) "Negative" symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses (it must be clear that these are not due to depression or to neuroleptic medication) [8].

1.2 ASSESMENT OF SEVERITY OF SYMPTOMS

In this study MADRS is used to assess depression and PANSS is used to assess the severity of symptoms of schizophrenia .Based on the individual scoring of patients, whether the patient is treatment resistant or not is defined.

1.2.1 Montgomery–Asberg Depression Rating Scale (MADRS)

The clinician-rated Montgomery and Asberg Depression Rating Scale (MADRS) was developed in the late 1979 by British and Swedish researchers as an adjunct to the Hamilton Rating Scale for Depression (HAMD) and this 10-item scale was designed to be sensitive to the effects of antidepressant medications, primarily tricyclic antidepressants (TCAs).Because this scale was Rating Scales for Depression never updated or modified, it does not target reverse neurovegetative symptoms. It is

commonly used in clinical studies and in clinical practice, administered weekly. Structured interview guides for the MADRS have been developed by a number of investigators of Reliability Internal Consistency. The MADRS appears to be a one dimensional scale, more focused toward psychological, as opposed to somatic aspects of depression. The internal consistency of the MADRS is considered very high, given the high correlation between all items (r = 0.95).

In a recent psychometric re-analysis of primary efficacy measures derived from a trial on citalopram efficacy in maintenance therapy of elderly depressed patients, the internal consistency of the MADRS, was found to be more superior to that of the HAM-D- 17. Inter-rater Reliability One of the original goals of the MADRS was to obtain an instrument that could be used by both psychiatrists and professionals without a specific or with minimal psychiatric training. From the original report of the MADRS, the inter-rater reliability ranged from 0.89 to 0.97. However, in a German study, significant differences resulted when the same patient was rated by various groups of caregivers (psychiatrists, psychologists, students, and psychiatric nurses). Validity Correlation of MADRS has been shown to be generally high or very high with the HAM-D (between 0.80 and 0.90), RDC (0.70), and with IDS-C (0.81) .Cut-Off Scores A score greater than 30 or 35 on the MADRS indicates severe depression, while the score of 10 or below indicates remission. Zung Self-Report Depression Scale [9].

1.2.2 POSITIVE AND NEGETIVE SYNDROME SCALE (PANSS)

One of the most widely used measures of psychopathology of schizophrenia in clinical research is the Positive and Negative Syndrome Scale (PANSS). The 30- item PANSS was developed originally for typological and dimensional assessment of patients with schizophrenia and was conceived as an operational zed, change-sensitive instrument that offers balanced representation of positive and negative symptoms and estimates their relationship to one another and to global psychopathology by Stanley Kay, Lewis Opler, and Abraham Fiszbein in 1987. It consists of three subscales measuring the severity of Positive Symptoms (seven items), severity of Negative Symptoms (seven items), and General Psychopathology (16 items).

The PANSS is typically administered by trained clinicians who evaluate patients' current severity level on each item by rating one of seven options (scores) representing

increasing levels of severity. The administration generally takes 30 to 60 minutes, depending on the patient's level of cooperation and severity of symptoms. The PANSS has demonstrated high internal reliability, good construct validity, and excellent sensitivity to change in both short term and long term trials. However, despite extensive psychometric research on the PANSS, until a recent Item Response Analysis (IRT) it was unclear how individual PANSS items differ in their usefulness in assessing the total severity of symptoms. All 30 items of this scale are rated on a 7-point scale (1 = absent; 7 = extreme). There are 3 subscales of the PANSS, the Positive Symptom subscale, the Negative Symptom subscale and the General Psychopathology subscale. The PANSS was developed with a comprehensive anchor system to improve the reliability of ratings. The 30 items are arranged as seven Positive subscale items (P1 - P7), seven Negative subscale items (N1 - N7), and 16 General Psychopathology items (G1 - G16). Each item has a definition and a basis for rating.

The interviewer must be trained to a standardized level of reliability for conducting the interview. PANSS rater, was required to obtain rater certification through Ortho-McNeil Janssen Pharmaceuticals, Incorporated, and to achieve interpreter reliability with an interclass correlation coefficient (95% CI) = 0.80 with the "Expert consensus PANSS" scores [10].

1.2.2.1 SCORING

As 1 rather than 0 is given as the lowest score for each item, a patient cannot score lower than 30 for the total PANSS score. Scores are often given separately for the positive items, negative items, and general psychopathology. In their original publication on the PANSS scale, Stanley Kay and colleagues tested the scale on 101 patients with schizophrenia and the mean scores were,

- Positive scale = 18.20
- Negative scale = 21.01
- General psychopathology = 37.74 [10]

1.3 MANAGEMENT

1.3.1 MANAGEMENT OF TRD

Treatment-resistant depression, a complex clinical problem caused by multiple risk factors, is targeted by integrated therapeutic strategies, which include optimization of medications, a combination of antidepressants, switching of antidepressants, and augmentation with non-antidepressants, psychosocial and cultural therapies, and somatic therapies including electroconvulsive therapy, repetitive transcranial magnetic stimulation, magnetic seizure therapy, deep brain stimulation, transcranial direct current stimulation, and vagus nerve stimulation. As a corollary, more than a third of patients with treatment-resistant depression tend to achieve remission and the rest continue to suffer from residual symptoms. The latter group of patients needs further study to identify the most effective therapeutic modalities. Newer biomarker-based antidepressants and other drugs, together with non-drug strategies, are on the horizon to address further the multiple complex issues of treatment-resistant depression [11].

1.3.1.1 APPROACH TO PATIENTS WITH TREATMENTRESISTANT DEPRESSION

Patient with depression fails to respond to at least 8 weeks of antidepressant therapy at an adequate dosage.

Confirm diagnosis.

Confirm medication adherence. Consider serum blood levels (primarily for TCAs).

Rule out organic causes of depression.

Maximize treatment of complicating co morbid diagnoses

Switch to another antidepressant or augment current medication with CBT, Bupropion, or buspirone. Consider psychiatric consultation.

Switch to a different pharmacologic class of antidepressant (e.g., TCA, mirtazapine), or augment current medication with lithium or triiodothyronine.

Switch to tranylcypromine or extended release venlafaxine plus mirtazapine. Seek psychiatric consultation. Consider ECT.

{Algorithm for management of treatment resistant depression (CBT = cognitive behaviour therapy; ECT = electroconvulsive therapy; TCA = tricyclic antidepressant.)}[12].

1.3.1.2 Optimization of antidepressants

The two core features of this strategy are to optimize dosage and duration of antidepressant therapy for patients who have experienced only partial improvement. The advantages of this strategy are to capitalize on the natural history of episodic depression which remits over time and to counteract the tendency of some patients to discontinue the antidepressant prematurely [13].

1.3.1.3 Switching strategies

The switching approach mainly involves discontinuing an ineffective antidepressant and starting a new antidepressant from a similar or different class in patients with treatment resistant depression. The advantages of this strategy are improved adherence, reduced medication costs and fewer drug interactions [14].

1.3.1.4 Combination of antidepressants

Combination therapy involves the addition of a second antidepressant agent from a different class to the therapeutic regimen of patients with treatment-resistant depression. The additional antidepressant is used for 12 weeks or even months in

optimum doses. Various types of combination are reported in the literature, but the most common are TCA + SSRI followed by, e.g., venlafaxine + TCA, SSRI + SSRI, and SSRI + venlafaxine. Venlafaxine +mirtazapine are frequently used in clinical practice, and this combination produces a good response in patients with difficult-to-treat depression, which is attributed to the synergistic action of this combination [15].

1.3.1.5 Augmentation strategies

Augmentation therapy involves adding a second agent (but one that is not routinely regarded as an antidepressant) to the therapeutic regimen when there is only a partial response to the primary antidepressant agent. The reported strength of recommendation for augmentation or switching is best supporting evidence. Various augmenting agents, including lithium, atypical antipsychotics, thyroid hormone, pindolol, buspirone, dopamine agonists, sex steroids, glucocorticoid-specific agents, herbal products, and newer anticonvulsants, have been used in patients with treatment-resistant depression [16].

1.3.1.6 Electroconvulsive therapy

ECT is a recognized mode of treatment for a variety of mental disorders, including treatment resistant depression. ECT is still the most consistently effective in patients with treatment resistant depression, with a response rate of 50%–70%.30[21]. Furthermore, ECT remains the treatment of first choice for the most severe, incapacitating forms of treatment resistant depression, though the strength of the recommendation of ECT is level C[20].Surprisingly, relapse rates are significantly higher in patients with treatment resistant depression after a successful course of therapy [17].

1.3.1.7 Other somatic therapies

These reversible but more invasive therapies were developed to avoid the adverse effects and complications of ECT and at the same time to be more effective in treatment resistant depression. rTMS and VNS are approved by the US Food and Drug Administration for the treatment of intractable seizure disorders and treatment-resistant depression. However, with regard to treatment resistant depression, other neuromodulation therapies, including DBS, magnetic seizure therapy, and tDCS, are in the experimental stages [18].

1.3.1.8 Psychotherapy

A variety of psychotherapeutic techniques can be used to treat depression, including CBT, interpersonal psychotherapy, nondirective counselling, befriending, problem solving therapy, psychodynamic psychotherapy, group psycho education, cognitive behavior analysis and also exercise [19]. However, evidence regarding the effectiveness of psychotherapeutic techniques in patients with treatment resistant depression is limited.

In summary, 70% of patients with major depression respond to initial antidepressant therapy, leaving 30% of patients who are refractory to treatment and therefore need special treatment-resistant depression management strategies. Twenty-five percent of patients with treatment-resistant depression tend to respond to optimization and combined treatment paradigms and another 50% of patients are reported to respond to switching therapeutic options. Augmentation strategies target the remaining 25% of patients suffering from treatment-resistant depression, with inconsistent outcomes. Overall, although there is no strict compartmentalization of treatment response and remission rate in the population with treatment-resistant depression, about one third of patients with the disorder continue to be resistant to available therapeutic options, and hence pose a major therapeutic challenge to mental health experts [11].

1.3.2 MANAGEMENT OF TRS

The goals and strategies of treating a patient with schizophrenia vary according to the phase and severity of illness. In the acute phase, the goal is to reduce or eliminate psychotic symptoms and improve functioning. During stabilization, the goal is to provide support to decrease the risk of relapse, increase the patient's adaptation to life in the community, and consolidate remission of symptoms. In the stable phase, the goal is to ensure that the patient maintains and improves his or her level of functioning and quality of life, and to treat any re-emerging psychotic symptoms, while adverse-effect monitoring and management continues. Second-generation antipsychotics (SGAs) (with the exception of clozapine) have become the agents of first choice in the treatment of schizophrenia, and most practice guidelines and consensus statements support this recommendation. The major advantage of atypical antipsychotics may be in their side effect profiles with respect to motor effects, as they generally have better overall tolerability than the FGAs [20].

Risperidone fulfils the atypical criterion of having a low incidence of EPS at low to moderate doses. The mean optimal dose in parallel, fixed-dose studies was 4 to 6 mg daily. At doses greater than6mg daily, risperidone's profile is more similar to that of an FGA. Because risperidone appears to lose its atypical profile at higher doses, the lowest possible dose should be used in treatment. This may include gradual dose titration downward if patients do not respond initially, rather than upward titration as has been the traditional approach to dosing antipsychotics [21-23].

Olanzapine has a very low incidence of EPS when used within the approved dose range of 10 to 20 mg daily. However, many patients are being treated at doses above the currently recommended limit in the approved product labelling of 20 mg/day. Quetiapine is an efficacious antipsychotic with an excellent EPS profile. Although contrary to efficacy studies, doses above 500 mg are often used to achieve optimal effects, with dose titration to 800 mg/day being a common occurrence. From a clinical perspective, the optimal daily quetiapine dose appears unclear [24].

Ziprasidone 40 to 160 mg/day appears to have efficacy similar to other SGAs, with response rates increasing at doses greater than 80 mg daily. Aripiprazole has established efficacy at 15 to 30 mg/day. Both aripiprazole and ziprasidone have significantly less potential to produce weight gain than other SGAs [25] .

The first is inadequate duration of treatment. It is accepted that a proportion of patients have a delayed response to clozapine (Meltzer, 1992). Meltzer concluded that 30% would respond by 6 weeks, a further 20% by 3 months and an additional 10–20% by 6 months. Therefore, it seems reasonable to try clozapine monotherapy for 6 months. This leaves a residue of 30% of patients for whom it must be decided whether to persevere with clozapine [26].

The second factor is inadequate dosage. Clozapine dosage can be a relatively complicated issue. In particular, there is no meaningful relationship between clozapine plasma levels and clinical response. However, there is a consensus in the literature that a plasma level of about 350–450ng/ ml has to be attained before the patient is considered to be non-respondent to clozapine (Perry *et al*, 1991; Patien*t al*, 1994).[26]

Clozapine is also subject to considerable metabolism by the cytochrome P450 (CYP) enzyme system (Aitchison et al, 2000). There are numerous variants of the genes encoding the CYP enzyme family within the general population, resulting in complex individual genetic profiles and a variable response to drugs metabolized by these enzymes (Ma et al, 2004). † Therefore, in clinical practice, patients can be very susceptible to side-effects at drug dose levels that appear to be below the threshold for clinical efficacy [26].

1.3.2.1 Pharmacotherapy of Treatment Resistance Schizophrenia – Algorithm

Clinical scenario: No adequate response to an initial trial with antipsychotics.

Before assuming non response, the following issues should be checked.

- Is the underlying diagnosis of a schizophrenic disorder correct?
- Are there relevant co morbidities?
- Is there a possible non-compliance in terms of medication intake?
- Was a sufficient dose of the antipsychotic achieved?
- Was the duration of the treatment sufficiently long?(at least 2-4 weeks at the target dose)
- Were sufficient plasma level achieved?
- Do adverse effects mask a response?

High dose treatment or switch off the antipsychotic drug

High dose treatment	Switch off antipsychotics
In a randomized clinical trials, there was no superiority of high dose medication (e.g. deficient as higher than the label dose) in comparison to administration of a standard dose for the majority of patients.	In studies with control group, the superiority of switching strategies was rather low overall, however there is slightly more evidence for a switch off the antipsychotics drug than for a high dose treatment based on studies without a control group. Drugs should be switched preferentially to an antipsychotic with a different receptor binding profile.

Medication with Clozapine

- Should be considered after non response to at least two trials with antipsychotic agents minimum treatment duration: eight weeks, plasma level guided

Combination and augmentation strategies

- Currently there is no sufficient convincing evidence to recommend such strategies, generally an antipsychotic monotherapy should be sough primarily.
- Utilization preferably for treating specific target symptoms (eg: Benzodiazepines for agitated patients or antidepressant affective symptoms.
- For combination treatment two antipsychotics with a different receptor binding profile should be chosen.

In the clinical practice of today, treatment-resistance cannot be categorically evaluated according to response, or lack thereof, to drug treatment. Setting forth Andresen's ideas on the concept of remission, we are closer to operational dimensional models that integrate the idea of continuum, and we speak of a lack of sufficient response. We believe that this concept should be more inclusive in its current vision of treatment resistant schizophrenia, since it could contribute a notion of continuum with response levels up to recovery of premorbid functioning, with regard to the individual's life expectations. Furthermore, it takes up the ideas of Brenner et al and Meltzer by integrating different pharmacological approaches, without denying the importance of drugs, while hoping for advances in research on pro-cognitive compounds, antipsychotic drugs, etc., which will mark new therapeutic milestones.

1.4 STUDY OF ADVERSE DRUG REACTIONS.

All drugs with the ability to produce a desired therapeutic effect also have the potential to cause unwanted adverse effects. The WHO defines ADR as 'A response to a drug that is noxious, unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of diseases or for modification of physiological function.

1.4.1 TYPES OF ADR

According to Rawlings Thomson system, ADR is classified in to different types as,

1. Type A: They are normal but quantitatively exaggerated pharmacological effect of the drug.
2. Type B: They are qualitatively abnormal effects which appear unrelated to the drugs pharmacology.
3. Type C: They occur with continuous use of certain drugs, which is related to the cumulative dose of the drug and are rarely occurring.
4. Type D: This reaction occurs usually within a short period after the stoppage of the drug.
5. Type E: They occur soon after the withdrawal of the drug.
6. Type F: These are very common and dose related, occurs due to inappropriate use of drugs or due to treatment failure.

The common ADRs shown by antipsychotics and antidepressants are extra pyramidal symptoms, metabolic syndrome, inappropriate prolactin level, sexual problems etc.

Naranjo scale and WHO causality assessment scales are mainly used to evaluate the ADR.

1.4.2 NARRANJO SCALE

The Naranjo algorithm, Naranjo Scale, or Naranjo Nomo gram is a questionnaire designed by Naranjo *et al.* for determining the likelihood of whether an ADR (adverse drug reaction) is actually due to the drug rather than the result of other factors. Probability is assigned via a score termed definite, probable, possible or doubtful. Values obtained from this algorithm are sometimes used in peer reviews to verify the validity of author's conclusions regarding adverse drug reactions. It is also called the Naranjo Scale or Naranjo Score.

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AIMS
&
OBJECTIVES

2. AIM & OBJECTIVES

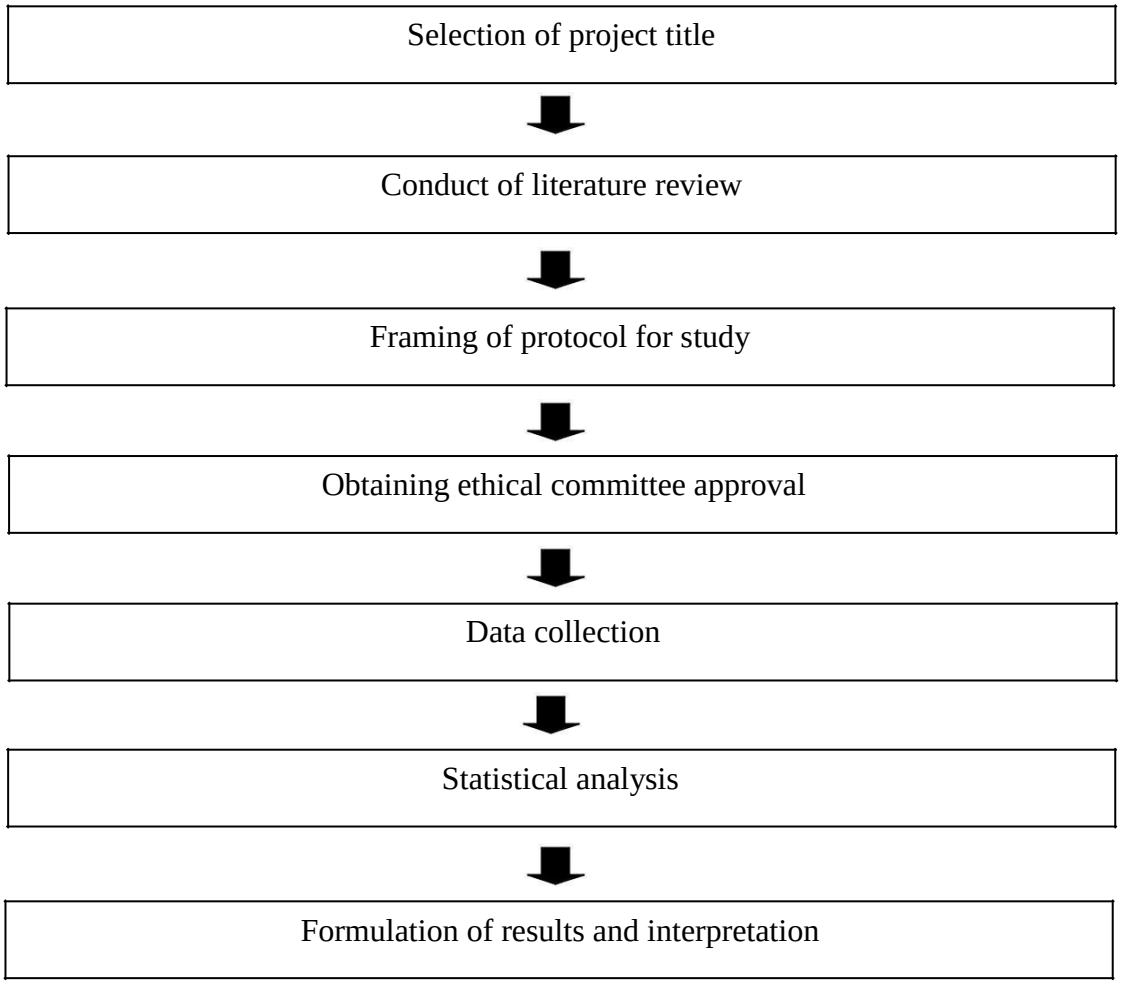
2.1 Aim:

To evaluate the demographic profile and management of treatment resistant schizophrenia and treatment resistant depression in psychiatric department.

2.2 Objectives:

1. To evaluate the demographic profile of TRS and TRD in psychiatric patients.
2. To assess the treatment modalities in managing TRS and TRD patients.
3. To monitor the adverse drug events associated with drug therapy**.**

2.3 Plan of study



REVIEW OF LITERATURE

3. REVIEW OF LITERATURE

3.1 The Combined Treatment of Venlafaxine and Quetiapine for Treatment-Resistant Depression: A Clinical Study

Xiaoyi Li, M.D. et al (2013) conducted a randomized control trial on TRD patients and studied the efficacy and safety of combined venlafaxine and quetiapine treatment for treatment-resistant depression (TRD) by dividing 95 TRD patients into two treatment groups: a combined venlafaxine (225 mg/day) and quetiapine (400mg/day) group and a venlafaxine only (225 mg/day) group for 8 weeks. Efficacy was assessed with the Hamilton Rating Scale for Depression, 17 items (Ham-D–17) and the Hamilton Rating Scale for Anxiety (Ham-A); safety was assessed with the Treatment-Emergent Symptom Scale (TESS). All data were represented as means (standard deviations [SD]) and analyzed with SPSS 12.0 software (Chicago, IL, U.S.). x^2 and t-tests were applied, and $\infty < 0.05$ was considered to be statistically significant in all cases. The two groups showed significant differences for the Ham-D–17 and Ham-A and no differences on the TESS. The present study showed that a combined treatment of venlafaxine and quetiapine provided benefits for TRD patients beyond those seen with venlafaxine alone. Also, a target venlafaxine dose of 225 mg/day was safe for patients in combination with quetiapine at a dose of 400 mg/day.

3.2 Role of Amisulpiride Augmentation in Treatment Resistant Major Depressive Disorder: An Open Label Study from North India

Mansoor Ahmad Dar et al (2015) evaluated whether augmentation with amisulpride was effective and tolerable in patients of major depressive disorder (MDD) who did not respond significantly to adequate trials of standard antidepressants. In this open labeled 6 weeks study, amisulpride was added to baseline antidepressant medication of treatment resistant patients of major depressive disorder. A total of 112 patients enrolled in the study with a mean age of 39.37 years out of which 83% completed the study. Over a period of 6 weeks, 71% patient showed response and 40% patient remitted ($p<0.001$) with a mean amisulpride dose of 135.31 mg/day. The mean decrease in HAM-D17 score was 16.17 points. There was more than 2 point change in

mean CGI-S score from base line to endpoint. Common adverse effects were akathisia (4.64%), sleep disturbances (10.71%), restlessness (5.36%) and extra pyramidal side-effects (4.64%). The study concluded that augmentation of antidepressant drugs with low doses of amisulpride seemed to be effective and tolerable in patients of major depressive disorder who do not respond adequately to standard antidepressant medications.

3.3 Treatment-Resistant Depression: Therapeutic Trends, Challenges, and Future Directions

Khalid Saad Al-Harbi et al (2012) in a meta-analysis reviewed the therapeutic options for treating resistant major depressive disorder, as well as evaluated further therapeutic options. Those papers that directly addressed treatment options for treatment-resistant depression were extensively reviewed. This study described treatment-resistant depression, a complex clinical problem caused by multiple risk factors, was targeted by integrated therapeutic strategies, which include optimization of medications, a combination of antidepressants, switching of antidepressants, and augmentation with non-antidepressants, psychosocial and cultural therapies, and somatic therapies including electroconvulsive therapy, repetitive transcranial magnetic stimulation, magnetic seizure therapy, deep brain stimulation, transcranial direct current stimulation, and vagus nerve stimulation. It concluded that newer biomarker-based antidepressants and other drugs, together with non-drug strategies, are on the horizon to address further the multiple complex issues of treatment-resistant depression and treatment-resistant depression continues to challenge mental health care providers, and further relevant research involving newer drugs is warranted to improve the quality of life of patients with the disorder.

3.4 Effects of Risperidone Augmentation in Patients with Treatment-Resistant Depression: Results of Open-Label Treatment Followed by Double-Blind Continuation

Mark Hyman Rapaport et al (2006) investigated the longer-term efficacy of risperidone augmentation of serotonin-selective reuptake inhibitor treatment for resistant depression. In 57 in- and outpatient centers in three countries, they conducted a three-phase study with 4–6 weeks of open-label citalopram monotherapy, 4–6 weeks

of open-label risperidone augmentation, and a 24-week double-blind, placebo-controlled discontinuation phase. A total of 489 patients with major depressive disorder and 1–3 documented treatment failures entered the citalopram monotherapy phase (20–60 mg/day). Patients with <50% reduction in HAM-D-17 scores entered the risperidone augmentation phase (0.25–2.0 mg/day). Patients with HAM-D-17 ≤ 7 or CGIS ≤ 2 were randomized to risperidone or placebo augmentation. The primary outcome was time to relapse during the double-blind phase. During citalopram monotherapy, 434 patients had <50% HAM-D-17 reduction; 299 (68.9%) were fully nonresponsive (<25% reduction) and 135 were partially nonresponsive (25–49% reduction). Of the 386 nonresponders who entered the augmentation phase, 243 remitted and 241 entered the double-blind phase. Median time to relapse was 102 days with risperidone augmentation and 85 days with placebo (NS); relapse rates were 53.3 and 54.6%, respectively. In a post hoc analysis of patients fully nonresponsive to citalopram monotherapy, median time to relapse was 97 days with risperidone augmentation and 56 with placebo (p =0.05); relapse rates were 56.1 and 64.1%, respectively (p ≤ 0.05). This large international multicenter study demonstrated that risperidone augmentation of citalopram was a reasonable and safe strategy that was helpful for some patients with treatment-resistant major depressive disorder.

3.5 Advances in the Management of Treatment-Resistant Depression

Paul E. Holtzheimer (2010) in this article defined and discussed the epidemiology of TRD, reviewed the current approaches to its management, and then provided an overview of several developing interventions. Papers that directly addressed treatment resistant depression were analyzed. In this study they concluded that advances in the management of TRD included the development of a number of novel pharmacological agents, many of which target systems outside the monoamines, as well as several focal neuromodulation techniques and overall, there is optimism that these strategies will lead to antidepressant treatments to help achieve and sustain remission in a greater number of depressed patients. The study stated that progress to date has been limited: despite encouraging preliminary results, none of the novel drugs are yet established for clinical use; the two FDA-approved brain stimulation therapies (VNS and TMS) are associated with relatively low response and remission rates, and neither has shown efficacy in those patients with the most extreme forms of treatment-resistant depression

(i.e., more than six treatment failures in the current episode); and data on the remaining brain stimulation approaches are far too preliminary to draw meaningful conclusions regarding safety and efficacy.

3.6 Pharmacologic Approaches to Treatment Resistant Depression: A Re-examination for the Modern Era

Noah S. Philip et al (2010) in this review surveyed literature on the diagnosis and pharmacological management of TRD in light of recent developments. Evidence regarding commonly used treatment options is critically examined and key recommendations are offered. The review ends by considering drugs acting on the melatonin, acetylcholine, and glutamate systems that hold promise as future options for TRD. This review says that currently available treatments have limited efficacy for TRD, a state of affairs that is complicated by a lack of consensus on the definition of TRD itself and although there is no clear "magic bullet" to address TRD, there are a wide variety of pharmacological options available with established, even if modest, efficacy. This articles explains several novel therapeutic options, targeting neurotransmitter systems outside of the standard monoamine hypothesis that are currently being investigated as promising alternatives. This review suggest that increasing recognition of the role of inflammation in depression, one can also hope that agents affecting these processes may prove to have utility for TRD. Ultimately they opt better understanding of the basic pathophysiology of TRD that will be needed to develop better-targeted and more effective treatments.

3.7 Cognitive and Psychosocial Improvements Following Aripiprazole Augmentation of SSRI Antidepressant Therapy in Treatment Refractory Depression: A Pilot Study

Tracy L. Greer et al (2013) with this study evaluated depressive symptom severity, cognitive function, and psychosocial function before and after six weeks of open-label aripiprazole augmentation treatment in patients with MDD who did not fully respond to selective serotonin reuptake inhibitor treatment. Participants endorsed difficulty with concentration and decision-making at study entry. Participants were maintained on their entry-level dose of SSRI and a flexible dose of 5 mg to 15 mg aripiprazole was added to their SSRI for 6 weeks. Participants started at 5 mg and went up to 15 mg

only if clinically indicated and not contraindicated due to adverse effects. Participants were assessed for possible abnormal involuntary movements or extrapyramidal symptoms at every visit. The primary aim of the study was to determine the effect of aripiprazole augmentation on depressive symptom severity, psychosocial function and cognitive function. Changes in depressive symptom severity and psychosocial function were assessed via t-tests. The results of this study support significant functional improvements, in addition to significant reductions in depressive symptoms, in quality of life, psychosocial function, and executive functioning following aripiprazole augmentation in MDD. In addition, aripiprazole augmentation was generally well-tolerated.

3.8 Atypical Antipsychotic Augmentation for Treatment- Resistant Depression: A Systematic Review and Network Meta-Analysis

Xinyu Zhou et al (2015) performed a network meta-analysis, which integrates direct and indirect evidence from randomized controlled trials (RCTs), to investigate the comparative efficacy and tolerability of adjunctive atypical antipsychotics for treatment-resistant depression (TRD). Systematic searches resulted in 18 RCTs (total n = 4422) of seven different types and different dosages of atypical antipsychotics and a placebo that were included in the review. The review observed that all standard-dose atypical antipsychotics were significantly more efficacious than placebo in the efficacy (standardized mean differences [SMDs] ranged from -0.27 to -0.43). There were no significant differences between these drugs. Low-dose atypical antipsychotics were not significantly more efficacious than the placebo. In terms of tolerability, all standard-dose atypical antipsychotics, apart from risperidone, had significantly more side-effect discontinuations than placebo (odds ratios [ORs] ranged from 2.72 to 6.40). In terms of acceptability, only quetiapine (mean 250–350 mg daily) had significantly more all-cause discontinuation than placebo (OR = 1.89). In terms of quality of life/functioning, standard dose risperidone and standard-dose aripiprazole were more beneficial than placebo (SMD = -0.38; SMD = -0.26, respectively), and standard-dose risperidone was superior to quetiapine (mean 250–350 mg daily). Study concluded that all standard-dose atypical antipsychotics for the adjunctive treatment of TRD are efficacious in reducing depressive symptoms. Risperidone and aripiprazole also showed benefits in improving the quality of life of patients.

3.9 Treatment-Resistant Depression in Primary Care across Canada

Sakina J Rizvi et al (2014) conducted a study to investigate the prevalence of TRD and to evaluate its clinical characterization and management, compared with non-resistant depression, in primary care centres. They completed a case report on a consecutive series of patients with major depressive disorder (n = 1212), which captured patient demographics and comorbidity, as well as current and past medication. The result showed that using failure to respond to at least 2 antidepressants (ADs) from different classes as the definition of TRD, the overall prevalence was 21.7%. There were no differences in prevalence between men and women or among ethnicities. Patients with TRD had longer episode duration, were more likely to receive polypharmacy (for example, psychotropic, lipid-lowering, and antiinflammatory agents), and reported more AD related side effects. Higher rates of disability and comorbidity (axes I to III) were associated with treatment resistance. Obesity and being overweight were also associated with treatment resistance. In summary, they concluded that TRD is prevalent, posing a significant issue, owing to its association with functional and symptom burden and the management of patients within a primary care sample from across Canada mostly followed clinical guidelines regarding AD choice, duration, and treatment strategies.

3.10 Somatic Therapies for Treatment Resistant Depression: ECT, TMS, VNS, DBS

Cristina Cusin et al (2012) reviewed the literature for articles reporting results for clinical trials in particular efficacy data, contraindications and side effects of somatic therapies including electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), vagal nerve stimulation (VNS) and deep brain stimulation (DBS). A literature search was performed using PubMed, Ovid Medline, Cochrane Database of Systematic Reviews and PsychINFO for articles published between 1990 and July 2011. The aim of this paper was to review new somatic therapies utilized in the treatment of TRD in comparison with electroconvulsive therapy (ECT), considered the “gold standard” for patients with TRD. The study showed that each of these devices has an indication for patients with different level of treatment resistance, based on acuteness of illness, likelihood of response, costs and associated risks. ECT is widely available and its effects are relatively rapid in severe TRD, but its cognitive adverse effects may be

cumbersome. TMS is safe and well tolerated, and it has been approved by FDA for adults who have failed to respond to one antidepressant, but its use in TRD is still controversial as it is not supported by rigorous double-blind randomized clinical trials. The options requiring surgical approach are VNS and DBS. They concluded that each method have its own advantages and side effects for the patients and need further studies.

3.11 Augmentation Treatments with Second-generation Antipsychotics to Antidepressants in Treatment-resistant Depression

Masaki Kato et al (2013) reviewed the efficacy and tolerability of SGA augmentation when added to antidepressant therapy for treatment-resistant MDD patients in acute phase studies published to date. They studied meta-analysis and randomized control trial of various authors on "Second-generation Antipsychotic Augmentation in Treatment-resistant Depression". They concluded based on clinically evaluated evidence that, SGAs may act as a successful adjunctive medical agent for patients who fail to respond to pharmacological monotherapy with antidepressants. The SGAs evaluated in this review, including aripiprazole, olanzapine, quetiapine and risperidone, have varying degrees of efficacy in TRD patients and account for approximately a -3-point difference on rating scales for depression and approximately a 10 % improvement in remission rate compared with placebo augmentation, although there is no clear evidence to recommend one over the others. They concluded that each SGA has particular adverse properties that could be severe, leading patients to discontinuation from the treatment or could be mild with fewer risks of discontinuation. The review suggest risk and benefit assessment when clinicians are considering subsequent pharmacotherapy following failed treatment with antidepressants.

3.12 Pharmacological Management of Treatment Resistant Depression: A Clinical Review

Noel Kennedy et al (2003) in this paper reviewed evidence for pharmacological approaches used in treatment resistant depression. Electronic literature searches were performed using Medline and Psychlit using broad search terms relating to TRD. Study

says that agents that potentiate both serotonin and noradrenaline may allow more patients to achieve full remission. Attention must be paid to dose titration and length of treatment courses in TRD. Augmentation with lithium and switching within antidepressant class or between classes can often improve symptoms but efficacy of other augmentation approaches remains uncertain .Antidepressant combinations and addition of atypical antipsychotics can be useful but combinations of predominantly serotonergic antidepressants should be avoided. Electroconvulsive therapy retains an important role in TRD but pharmacological treatments need to be continued concomitantly. They conclude that good improvement is seen in TRD after vigorous antidepressant treatment but most patients continue to have lower grade symptomatology. Most subjects with TRD continue to be symptomatic even after vigorous antidepressant treatment with good improvement in the majority but few reaching asymptomatic status. Subjects with chronic depression in the NIMH Collaborative Depression Study tended to continue at a lower level of severity over time, more like dysthymia than chronic depression though recovery was possible even after an episode lasting many years. They suggest that the best approach in treatment of resistant depression appears to be vigorous pharmacological treatment with high dose single of combination antidepressant therapy combined with later intensive psychological approaches and careful follow-up to avoid recurrence.

3.13 Comparisons of the Efficacy and Tolerability of Extended-Release Venlafaxine, Mirtazapine, and Paroxetine in Treatment-Resistant Depression A Double-Blind, Randomized Pilot Study in a Chinese Population

Yiru Fang et al (2010) compared the efficacy and tolerability of antidepressants switch with extended-release venlafaxine (venlafaxine-XR), mirtazapine, and paroxetine in Chinese patients with major depressive disorder who had 2 consecutive unsuccessful antidepressant trials. In this one hundred fifty adult patients with treatment-resistant depression according to their medical records and/or response to current treatments were randomly assigned to receive fixed-dosage treatment of venlafaxine-XR 225 mg/d (n = 50), mirtazapine 45 mg/d (n = 55), or paroxetine 20 mg/d (n = 45) for 8 weeks. Here the primary outcome was the remission rates that were defined as a score 7 or lower on the 17-item Hamilton Rating Scale for Depression (HRSD-17). Secondary outcomes included the remission rate defined by the Self-

Rating Depression Scale of 50 or lower and the response rate defined by a 50% reduction or greater on the HRSD-17 total score, and the improvement of patients' general health functions. The completion rates were 82% for venlafaxine-XR, 81.8% for mirtazapine, and 82.2% for paroxetine. Only one patient in paroxetine arm discontinued the study owing to an adverse event. The remission rates based on the HRSD-17 were 42.0% for venlafaxine-XR, 36.4% for mirtazapine, and 46.7% for paroxetine. There were no statistical significances between treatment arms in remission rates. Similarly, there were also no significant differences between groups in secondary outcome measure. Venlafaxine-XR, mirtazapine, and paroxetine were equally effective in the treatment of Chinese patients with major depressive disorder who failed at least 2 previous antidepressant treatments. The study concluded that selecting any of these 3 antidepressants as a third-step antidepressant is a reasonable choice for this group of patients.

3.14 Management of Clozapine-Resistant Schizophrenia

Rob W. Kerwin & Anusha Bolonna (2005), suggested that the incidence of treatment resistance in schizophrenia (failure to respond to antipsychotic therapy) is about 20%. The National Institute for Clinical Excellence recommends that clozapine be used for schizophrenia resistant to another atypical antipsychotic. In this review, they focus on patients who are also resistant to clozapine given in adequate dosage for sufficient duration. They suggests that switching from clozapine to a previously untried atypical (e.g. olanzapine, risperidone, quetiapine) might be of benefit in partial treatment resistance. In more difficult cases, augmentation of clozapine with benzamides (sulpiride, amisulpride) and anti-epileptics (lamotrigine) shows some success. In extreme treatment resistance, a strategy is recommended that combines the proven best drug for the particular patient and psychosocial treatments. There is also reasonable evidence to suggest that augmentation strategies with sulpiride, amisulpride and lamotrigine are useful in treatment resistance, but no indication as to which patient will benefit from which strategy.

3.15 Risperidone in Treatment-Refractory Schizophrenia

Donna A. Wirshing et al (2000), conducted a four week, double blind, fixed dose comparison trial that was followed by a 4-week, flexible-dose phase. Sixty-seven

medication-unresponsive subjects were randomly assigned to treatment with risperidone (N=34) or haloperidol (N=33). Measures of clinical change were quantified by them using standard psychopathologic and neuromotor instruments. They suggested that risperidone demonstrated clinical efficacy superior to that of haloperidol on the total Brief Psychiatric Rating Scale (BPRS) after the first 4 weeks of treatment. Risperidone did not show any advantage over haloperidol after an additional 4 weeks. Overall improvement on the BPRS at 4 weeks was significantly better for the risperidone group (24%) than for the haloperidol group (11%). Risperidone-treated subjects were significantly less likely than haloperidol-treated subjects to require concomitant anticholinergic medication after 4 weeks (20% versus 63%); they also had significantly less observable akathisia (24% versus 53%) and significantly less severe tardive dyskinesia. Baseline characteristics that correlated significantly with risperidone response were positive symptoms, conceptual disorganization, akathisia, and tardive dyskinesia. They concluded that risperidone was better tolerated and more effective in a subset of patients with treatment-refractory schizophrenia. Positive psychotic symptoms and extrapyramidal side effects at baseline appear to be powerful predictors of subsequent response to risperidone.

3.16 Randomized Controlled Trial of Effect of Prescription of Clozapine Versus Other Second-Generation Antipsychotic Drugs in Resistant Schizophrenia

Shon W. Lewis et-al(2006), conducted a double blind study on 136 people aged 18–65 with DSM-IV schizophrenia and related disorders whose medication was being changed because of poor clinical response to 2 or more previous antipsychotic drugs. Participants were randomly allocated to clozapine or to one of the class of other SGA drugs (risperidone, olanzapine, quetiapine, amisulpride) as selected by the managing clinician. Outcomes were assessed blind to treatment allocation. One-year assessment were carried out in 87% of the sample. They assessed that treatment comparison showed no statistically significant advantage for commencing clozapine in Quality of Life score (3.63points; CI: 0.46–7.71; p = .08) but did show an advantage in Positive and Negative Syndrome Scale (PANSS) total score that was statistically significant (–4.93 points; CI:8.82 to 1.05; p = .013) during follow-up. They suggested that clozapine showed a trend toward having fewer total extrapyramidal side effects and at 12 weeks participants who were receiving clozapine reported that their mental health was

significantly better compared with those receiving other SGA drugs. In conclusion, in people with schizophrenia with poor treatment response to 2 or more antipsychotic drugs, there is an advantage to commencing clozapine rather than other SGA drugs in terms of symptom improvement over 1 year.

3.17 Pharmacotherapy for Treatment Resistant Schizophrenia

Meghan E Mcilwain, Jeff Harrison, Amanda J Wheeler, Bruce R Russell (2011), conducted a study that suggests that Clozapine has been shown to be more effective than other antipsychotics in treatment-resistant populations in however, the occurrence of adverse effects, some of which are potentially life-threatening, are important limitations. In addition to those who are intolerant to clozapine, only 30% to 50% experience clinically significant symptom improvement. This review describes the recent evidence for treatment strategies for people not responding to non-clozapine antipsychotic agents and people not responding or only partially responding to clozapine. In addition to people with treatment-resistant schizophrenia, studies suggest that clozapine may be useful for those at high risk of suicide or aggression. The adverse effects of clozapine are significant, ranging from acute events such as agranulocytosis to insidious weight gain and the onset of the metabolic syndrome. Many studies reported that clozapine treatment produced the greatest increase in BMI and/or body weight, closely followed by olanzapine.

3.18 Effectiveness of Second-Generation Antipsychotics in Patients with Treatment- Resistant Schizophrenia: A Review and Meta-Analysis of Randomized Trials

Miranda Chakos, M.D. et al (2001), conducted a review and meta-analysis of studies that compared the efficacy and tolerability of typical and second-generation antipsychotics for patients with treatment-resistant schizophrenia. A systematic search revealed 12 controlled studies (involving 1,916 independent patients), which were included in the review. The meta-analysis confirmed that treatment-resistant schizophrenic patients have more favourable outcomes when treated with clozapine rather than a typical antipsychotic, as reflected by Brief Psychiatric Rating Scale total score. The results of a meta-analysis indicated that clozapine exhibits superiority over

typical antipsychotics in terms of both efficacy (as measured by improvement in overall psychopathology) and safety (in terms of reduced extrapyramidal side effects). Of the 10 comparisons of second-generation versus typical antipsychotics, six found a significant difference that favoured the second-generation antipsychotic on measures of treatment efficacy; four found no significant difference between treatments. Five of the seven studies that compared clozapine to a typical antipsychotic medication in treatment-resistant patients found a significant difference favouring clozapine.

3.19 Clozapine, Olanzapine, Risperidone, and Haloperidol in the Treatment of Patients with Chronic Schizophrenia and Schizoaffective Disorder

Jan Volavka, et al (2002), conducted a double-blind trial, in 157 in patients with a history of suboptimal treatment response were randomly assigned to treatment with clozapine, olanzapine, risperidone, or haloperidol for 14 weeks (an 8-week escalation and fixed dose period followed by a 6-week variable- dose period). They suggests that Clozapine, risperidone, and olanzapine (but not haloperidol) resulted in statistically significant improvements in total score on the Positive and Negative Syndrome Scale. Improvements seen in total and negative symptom scores with clozapine and olanzapine were superior to haloperidol. The study reveals that atypical drugs, particularly olanzapine and clozapine, were associated with weight gain. They conclude that the effects of atypical antipsychotics in this population were statistically significant but clinically modest. The overall pattern of results suggests that clozapine and olanzapine have similar general antipsychotic efficacy and that risperidone may be somewhat less effective. Clozapine was the most effective treatment for negative symptoms.

3.20 The practical management of refractory schizophrenia – the Maudsley Treatment review and Assessment Team service approach

K. Beck et al (2014), conducted a study to describe the practical approach to the community management of treatment-resistant schizophrenia (TRS). They did a descriptive review of an approach to the assessment and management of patients with TRS, including the community titration of clozapine treatment, and a report of the management recommendations for the first one hundred patients assessed by the

Treatment Review and Assessment Team (TREAT). They suggested a standardized model for the community assessment, management and titration of clozapine. 137 patients have been referred to this service and 100 patients (72%) attended for assessment. Of these, 33 have been initiated on clozapine while fifteen have had clozapine recommended but have not wished to undertake clozapine treatment. Other management options recommended have included augmentation strategies and long-acting injectable antipsychotics. They concluded their study that the service had increased the number of patients receiving community assessment and initiation of clozapine by five-fold relative to the rate prior to the establishment of the service. The large number of referrals and high attendance rate indicates that there is clinical demand for the model. Systematic evaluation is required to determine the clinical and cost-eff ectiveness of this model and its potential application to other clinical settings.

3.21 Role of Aripiprazole in Treatment Resistant Schizophrenia

Nilfar Mossaheb, Rainer M Kaufmann (2012), conducted this study to evaluate the evidence for aripiprazole as a potential strategy in monotherapy or combination therapy for patients with treatment-resistant schizophrenia. Since no recommendation can be made on the basis of the currently available data as evidence for aripiprazole monotherapy and for the combination of aripiprazole with psychotropics other than clozapine is scant. The findings of four randomized controlled trials with respect to changes in psychopathology seem less conclusive. The most commonly found beneficial effects of this study are better metabolic outcomes and indicators of the possibility of reducing the clozapine dose. However, other side effects, such as akathisia, were repeatedly reported. This study suggests that combining aripiprazole with clozapine in clozapine-resistant or clozapine-intolerant patients seems to be worthy of further investigation from the pharmacological and clinical points of view.

3.22 Risperidone versus Clozapine in Treatment-Resistant Chronic Schizophrenia: A Randomized Double-Blind Study

G. Bondolfi et-al (2000), conducted this study to compare the short-term efficacy and safety of risperidone and clozapine in treatment-resistant chronic schizophrenic patients. In this controlled double-blind, multicenter study, 86 in patients with chronic

schizophrenia (DSM- III-R), who were resistant to or intolerant of conventional neuroleptics, were randomly assigned to receive risperidone or clozapine for 8 weeks after a 7-day washout period. After a 1-week dose-titration phase, doses were fixed at 6 mg/day of risperidone and 300 mg/day of clozapine for 1 week and then adjusted according to each patient's response. The final mean doses were 6.4 mg/day of risperidone and 291.2 mg/day of clozapine. Treatment efficacy and safety were evaluated with several well-known rating scales. Based on their study they noted that both risperidone and clozapine significantly reduced the severity of psychotic symptoms (scores on the Positive and Negative Syndrome Scale and the Clinical Global Impression scale) from baseline, with no significant between-group differences. At endpoint, 67% of the risperidone group and 65% of the clozapine group were clinically improved (reduction of 20% or more in total Positive and Negative Syndrome Scale score). Risperidone appeared to have a faster onset of action. In both groups extra pyramidal symptoms and other adverse events were few, and their severity was generally mild. Neither group showed evidence of a relation between drug plasma concentrations and clinical effectiveness and they concluded their study as Risperidone was well tolerated and as effective as medium doses of clozapine in patients with chronic schizophrenia who had been resistant to or intolerant of conventional neuroleptics.

3.23 Randomized controlled trial of occupational therapy in patients with treatment-resistant schizophrenia

Patrícia Cardoso Buchain et-al (2003), compared two groups of patients with TRS. The experimental group (EG) received psychopharmacological treatment with clozapine plus sessions of occupational therapy (OT) and the control group (CG) received only clozapine. To evaluate the outcome of the study, The Scale for Interactive Observation in Occupational Therapy (EOITO) was employed. The duration of the study was 6 months and patients were rated at baseline and monthly totaling 7 assessments. EOITO was independently applied by two occupational therapists with high reliability rates (Kappa=0.90, p=0.001). Repeated measures of analyses of variance and the evaluation of the standardized effect sizes were used for statistical analyses. The study showed that the EG showed that the OT intervention was effective along the whole period of observation, mainly from the 4th month to the end

of the study. This study concluded that in patients with TRS, the combination of OT and clozapine showed to be more effective than the use of clozapine alone. OT may represent an additional therapeutic option for patients with TRS.

3.24 Effectiveness of Clozapine Versus Olanzapine, Quetiapine, and Risperidone in Patients With Chronic Schizophrenia Who Did Not Respond to Prior Atypical Antipsychotic Treatment

Joseph P. McEvoy et al (2006), conducted a study that compares switching to clozapine with switching to another atypical antipsychotic in patients who had discontinued treatment with a newer atypical antipsychotic in the context of the Clinical Antipsychotic Trials for Interventions Effectiveness (CATIE) investigation. Ninety-nine patients who discontinued treatment with olanzapine, quetiapine, risperidone, or ziprasidone in phase 1 or 1B of the trials, primarily because of inadequate efficacy, were randomly assigned to open-label treatment with clozapine (N=49) or blinded treatment with another newer atypical anti- psychotic not previously received in the trial (olanzapine [N=19], quetiapine [N= 15], or risperidone [N=16]).The study suggests that time until treatment discontinuation for any reason was significantly longer for clozapine (median=10.5 months) than for quetiapine (median= 3.3), or risperidone (median=2.8), but not for olanzapine (median=2.7). Time to discontinuation because of inadequate therapeutic effect was significantly longer for clozapine than for olanzapine, quetiapine, or risperidone. The study reveals that at 3-month assessments, Positive and Negative Syndrome Scale total scores had decreased more in patients treated with clozapine than in patients treated with quetiapine or risperidone but not olanzapine. The study concludes that for these patients with schizophrenia who prospectively failed to improve with an atypical antipsychotic, clozapine was more effective than switching to another newer atypical antipsychotic.

3.25 Current Perspectives In The Treatment Of Resistant Schizophrenia

R.K.Solanki et al (2009), this study summarizes the current knowledge based on the diagnosis and management of treatment resistant schizophrenia. While the prevalence of treatment resistant schizophrenia is definition dependent, estimates have ranged from 30% to up to 60%. This study first looks into the various diagnostic criteria of

treatment resistant schizophrenia. Then the study reviewed about the pharmacotherapeutics of its management and they suggest that clozapine emerges to be the gold standard. In addition risperidone and high dose Olanzapine also emerge as clinically useful options. Other emerging adjunctive treatment options are equally addressed in this study. Though clozapine appears to emerge as the gold standard for treatment resistant schizophrenia, however it still lacks effect in some of the subjects. Nevertheless augmentation studies have shown promising results. Other atypical antipsychotics esp. Risperidone and high dose Olanzapine also show response in some resistant cases. Studies till date indicate that psychosocial interventions have important role in the management of the patients of treatment resistant schizophrenia and this field needs more exploration. The reason for this treatment resistance is not clearly addressed in this study, but the role of rapid metabolizers, pharmacogenetics and single nucleotide polymorphisms may explain the same in the time to come.

3.26 Clozapine v/s Conventional Antipsychotic Drugs For Treatment Resistant Schizophrenia: A Re-examination

Joanna Moncrieff (2003), conducted this study to re-evaluate the results of relevant trials by comparing clozapine with other conventional antipsychotics and thus investigating the sources of heterogenicity, since there exist a consensus that clozapine is more effective than conventional antipsychotic drugs for treatment resistant schizophrenia. She inspected individual studies with assessment of clinical relevance of results. Meta-regression analysis was performed to investigate sources of heterogeneity. Based on the examination of ten trials, recent large scale studies have not found a substantial advantage for clozapine, especially in terms of clinically relevant effect. Meta regressions showed that shorter study duration, financial support from a drug company and higher baseline symptoms score consistently predicted greater advantage of clozapine. And she concluded the study it may be inappropriate to combine studies in meta-analysis, given the degree of heterogeneity between their findings. The benefits of clozapine compared with conventional treatment may not be substantial.

3.27 Augmentation of Olanzapine in Treatment Resistant Schizophrenia

Mathias Zink (2005), claims up to 40% of patients with schizophrenic psychoses have symptoms that are resistant to monotherapy with antipsychotic drugs. In consequence, combinations of drugs are often used, especially based on the antipsychotic agents clozapine and Olanzapine because of their broad receptor-interaction profile. Thus with an aim of providing a critical overview of the published results of Olanzapine augmentation, he conducted this systemic review. He performed a systematic database search on MEDLINE and BIOSIS (Ovid), looking for publications on augmented therapeutic approaches involving Olanzapine, by using the search terms like "augmentation," "combination," "schizophrenia," "Olanzapine," and the names of other antipsychotic drugs and non-antipsychotic agents, including brand names, spanning publications from 1966 until the end of December 2004. Based on critical evaluation of data obtained he reach on an assumption, of 14 reports dealing with 8 different antipsychotic augmentation strategies (83 patients), only 1 trial, of sulpiride Olanzapine therapy, was performed in a randomized manner. Based on clinical observation, a significant number of the treatments led to favorable results. In contrast to adjuvant therapy with antipsychotic drugs, augmentation of Olanzapine with glycine, antidepressants or mood stabilizers was evaluated in well-designed clinical trials (8 publications, 989 patients), with distinct improvements of positive and/or negative symptoms reported. And then he concluded the review as the combination of Olanzapine with antidopaminergic atypical antipsychotic agents seems to follow a neurobiological rationale. The augmentation trials with nonantipsychotic agents, for example, mood stabilizers, were successful and showed that randomized and placebo-controlled trials are feasible. Therefore, systematic evaluations of antipsychotic agents as adjuvant therapy are possible as well as necessary to determine the benefits and risks of any new treatment strategy.

METHODOLOGY

4. METHODOLGY

4.1 Study Setting:

The study was carried out in KIMS Al Shifa Hospital located in Perinthalmanna at Malappuram district. It is a 750 bedded multispecialty tertiary level referral hospital. The hospital is unique and people from all over the country come and avail its facilities. The various specialties include general medicine, obstetrics and gynecology, pediatrics and neonatal, neurosciences, anesthesiology, orthopedics, radiology, nephrology, pulmonology and critical care, cardiology and cardiothoracic surgery, microbiology, pathology and hematology, laparoscopic surgery, ENT, dental and maxillofacial surgery, neurology, ophthalmology, physical medicine and rehabilitation, dialectology, surgical gastroenterology, oncology, psychiatry. The hospital is also equipped with modern diagnostic facilities like CT scan, MRI scan, ultra Sound sonography, digital subtraction angiography, treadmill, color doppler etc. The hospital also has twelve hi-tech operation theatres, Intensive Care Unit, intensive cardiac care unit, catheterization balloon valvuloplasty, coronary stenting, kidney transplantation unit with haemodialysis machines and an assisted reproductive technology center.

4.2 Study Design:

It is an observational descriptive study to determine the demographic profile and management strategies of treatment resistant schizophrenia and treatment resistant depression.

4.3 Study Period:

The study spanned over duration of 6 months, commencing from November 2016 to April 2017.

4.4 Ethics Clearance:

The study was approved by the ethics committee of Kims AlShifa hospital Pvt. Ltd and an official consent was provided by the concerned authority for the purpose of conducting the study. It was certified by the Institutional Ethical Committee met on 20th December 2017 and approved the proposal of the dissertation as per letter no KAS/ADMN/AC/EC/154/2017.

4.5 Study Criteria:

The patients for the study were selected on the basis of the following inclusion and exclusion criteria during the study period of 6 months.

4.5.1 Inclusion Criteria:

- Age between 18 – 65 years.
- Patients who can give informed consent.
- Patients satisfying the diagnostic criteria for treatment resistant schizophrenia.
- Patients satisfying the diagnostic criteria for treatment resistant depression**.**

4.5.2 Exclusion Criteria:

- Age below 18 years and above 65 years.
- Patients with epilepsy, other substantial organic or neurologic disease, or clinically relevant abnormal ECGs or laboratory tests.
- Patients with a history of alcohol or drug abuse within the previous 12 months.
- Patients with another psychiatric disorder as comorbid illness.

4.6 Study Tools

4.6.1 Data Collection Form:

A data collection form (Annexure III) was designed to collect information necessary for the study. The form consists of the following details:

1. Patient demographics.
2. Presenting symptoms
3. Physical examination.
4. Final diagnosis.
5. Past medical history.
6. Past medication history.
7. Family history.
8. Social history.
9. Symptom assessment.

10. Medication chart containing name of the drug, dose, route of administration and frequency, date started and date stopped.
11. Electroconvulsive therapy.
12. Laboratory reports.
13. Adverse drug reactions.

4.6.2. Informed Consent

The nature, type or intention of the study was explained to the patients by direct patient interaction. Participants were then given time to decide whether or not to participate. If they decided to participate, written consent was obtained. Patient consent form is included in Annexure

4.7. Sources of Data

- Patients case record.
- Patient's prescription.
- Direct interactions with physician.
- Montgomery Asberg Depression Rating Scale.
- Positive and Negative Syndrome Scale.

4.7.1. Data Collection

Demographic data, details of co morbid conditions etc were collected from patient's case records. Patient case records were reviewed to collect the details of disease, medications, social and family histories etc. Data relevant to the study were obtained and recorded using Hamilton depression rating scale and positive and negative syndrome scale.

The baseline characteristics were collected at the time of recruitment of patients in the study.

Scales used in data collection

- Montgomery Asberg Depression Rating Scale.
- Positive And Negative Syndrome Scale.

4.7.1.1 Patient case record

Patient demographics, co morbidities, social and family history were obtained from patient case record available in both electronic and written format maintained in the hospital.

4.7.1.2 Patients prescription

Electronic prescription were checked and data regarding current therapy and past medication were collected. Written prescriptions are obtained from patients during each hospital visit for cross verification.

4.7.1.3 Direct interaction with physician

Discussing the appropriateness of the therapy and the rationality of each drug based on evidence based literature review**.**

4.7.1.4. Montgomery Asberg Depression Rating Scale

Rating Clinician-rated

Administration time 10–15 minutes

Main purpose: To assess the severity of symptoms of depression

Population: Adults, adolescents and children

The MADRS was one of the rating scales developed to measure the severity of depressive symptoms, and is widely used today in both clinical and research settings. The scale consists of 10 items, each defined by a series of symptoms, and measures severity of depressive episodes. This scale would be more sensitive to the changes brought on by antidepressants and other form of treatment than the Hamilton Depression Rating Scale was.

Scoring

Each item is scored on a scale of 0 (not present) to 6 (severe), with a total score range of 0–60, where <19 indicates mild depression, 20–34 moderate depression and >34 severe depression.

4.7.1.5. Positive And Negative Syndrome Scale (PANSS)

Rating: Self or family report or clinician rated

Administration time 45 minutes

Main purpose: To assess severity of symptoms of schizophrenia.

Population: Adults and adolescents aged 15 and older.

PANSS is a medical scale used for measuring symptom severity of patients with schizophrenia. It is widely used in the study of antipsychotic therapy. The name refers to the two types of symptoms in schizophrenia, as defined by the American Psychiatric Association; positive symptoms, which refer to an excess or distortion of normal functions and negative symptoms, which represents a diminution or loss of normal functions. To assess a patient using PANSS, an approximately 45 minute clinical interview is conducted. The patient is rated from 1 to 7 on 30 different symptoms based on the interview as well as reports of family members or primary care hospital workers.

Scoring

The scale consist of a positive scale which contains 7 items (minimum score = 7, maximum score = 49), a negative scale with 7 items (minimum score = 7, maximum score = 49), and a general psychopathology scale which contains 16 items (minimum score = 16, maximum score = 112). Being considered "mildly ill" according to the Clinical Global Impressions approximately corresponded to a PANSS total score of 58, "moderately ill" to a PANSS of 75, "markedly ill" to a PANSS of 95 and "severely ill" to a PANSS of 116.

4.8. Study Procedure

The patients in Psychiatry department diagnosed with treatment resistant schizophrenia and treatment resistant depression were selected based on inclusion and exclusion criteria. Demographic profile of the patients were collected from their case files. The severity of symptoms of TRS patients were assessed using PANSS. The severity of symptoms of TRD patients were assessed using MADRS. Treatments were given to the patients according to their symptoms severity. Dose adjustments were done based on individual patient aspects. Effectiveness of the therapy were measured using PANSS and MADRS scale scorings. The collected data were analyzed, categorized and entered into Ms. Excel format. Statistical analysis of the collected details was done at the last stage of study.

4.9. Statistical Analysis

Type of sample test proposed to be used for determining conclusion

The collected data for the study were compiled and analyzed for drawing inferences employing statistical techniques. The test used was "Wilcoxon signed rank test". It is a non-parametric statistical hypothesis test used when comparing two related samples, matched samples or repeated measurements on a single sample to assess whether their population mean ranks differ.

The steps for calculation of Wilcoxon signed rank test is:

1. State the null hypothesis.

2. Calculate each paired difference, di = xi − yi, where xi, yi are the pairs of observations.

3. Rank the dis, ignoring the signs (i.e. assign rank 1 to the smallest |di|, rank 2 to the next etc.)

4. Label each rank with its sign, according to the sign of di.

5. Calculate W^+, the sum of the ranks of the positive dis, and W^-, the sum of the ranks of the negative dis. (As a check the total, $W^+ + W^-$, should be equal to n(n+1) /2 , where n is the number of pairs of observations in the sample).

$$Z = \frac{W - m_w \pm 0.5}{\sigma_w}$$

Where, $\sigma_w = \sqrt{\frac{n(n+1)(2n+1)}{6}}$

RESULTS

5. RESULTS

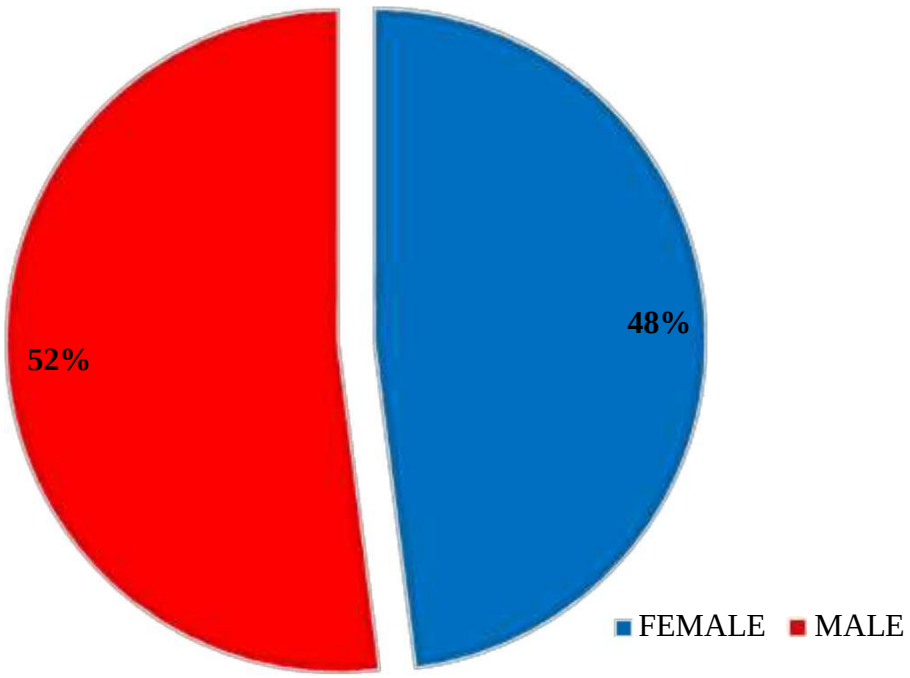
As per the inclusion and exclusion criteria, a total of 25 patients were enrolled in the study for treatment resistant schizophrenia and 27 patients were enrolled in the study for treatment resistant depression.

5.1 CLINICAL DEMOGRAPHICS

5.1.1 THE GENDER WISE DISTRIBUTION OF PATIENTS WITH TREATMENT RESISTANT SCHIZOPHRENIA:

Out of the data collected from 25 patients who visited at the Psychiatry department, 13 patients (52%) were males and 12 patients (48%) were females.

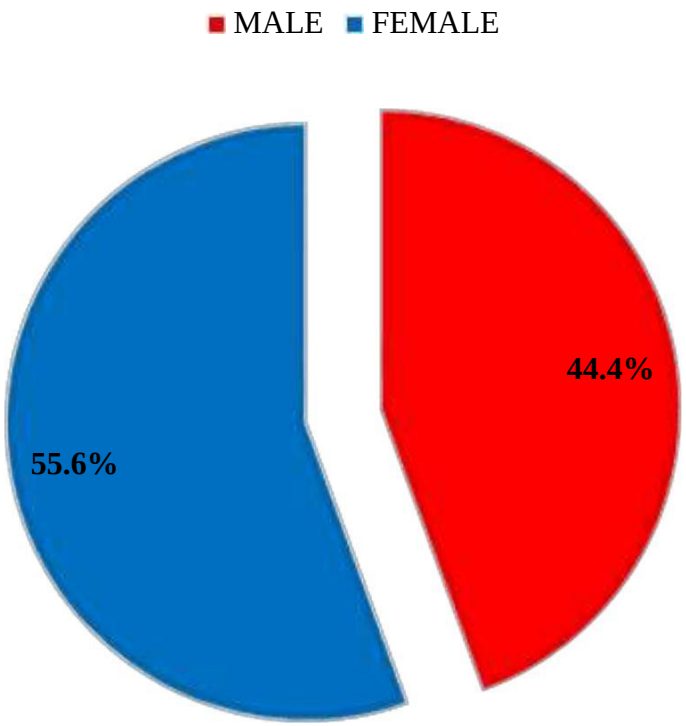
FIG. 1.GENDER WISE DISTRIBUTION OF TRS PATIENTS



5.1.2 THE GENDER WISE DISTRIBUTION OF PATIENTS WITH TREATMENT RESISTANT DEPRESSION:

Out of the data collected from 27 patients who visited the Psychiatry department, 12 patients (44.4%) were males and 15 (55.6%) females.

FIG. 2. GENDER WISE DISTRIBUTION OF TRD PATIENTS

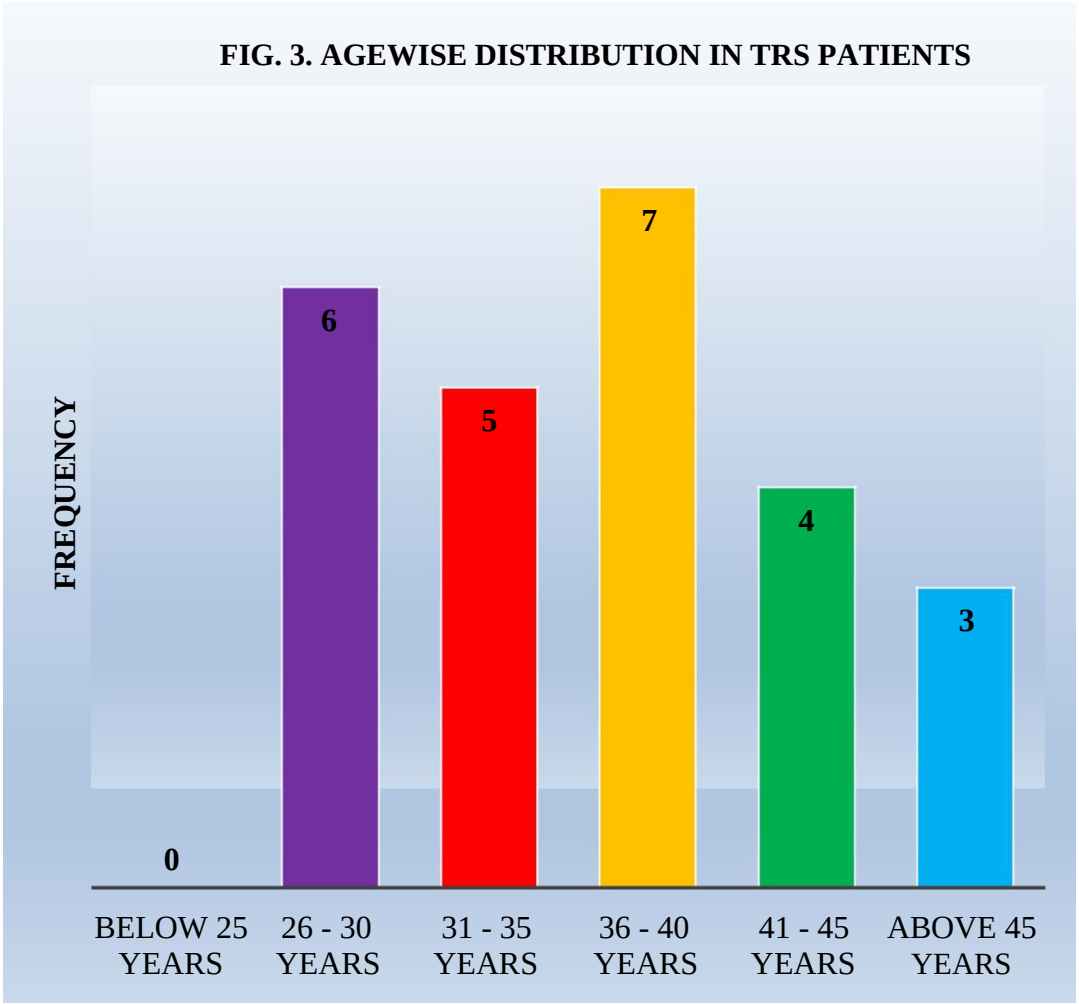


5.1.3 AGEWISE DISTRIBUTION OF THE PATIENTS WITH TREATMENT RESISTANT SCHIZOPHRENIA:

The mean age = 37.12 ± 7.79 years (Range- 26 to 57 years).

Age category: Below 25=0%, 26 to 30=24% (n=6), 31 to 35=20% (n=5), 36 to 40=28% (n=7), 41 – 45 =16% (n=4).and above 45 =12% (n=3).

FIG. 3. AGEWISE DISTRIBUTION IN TRS PATIENTS



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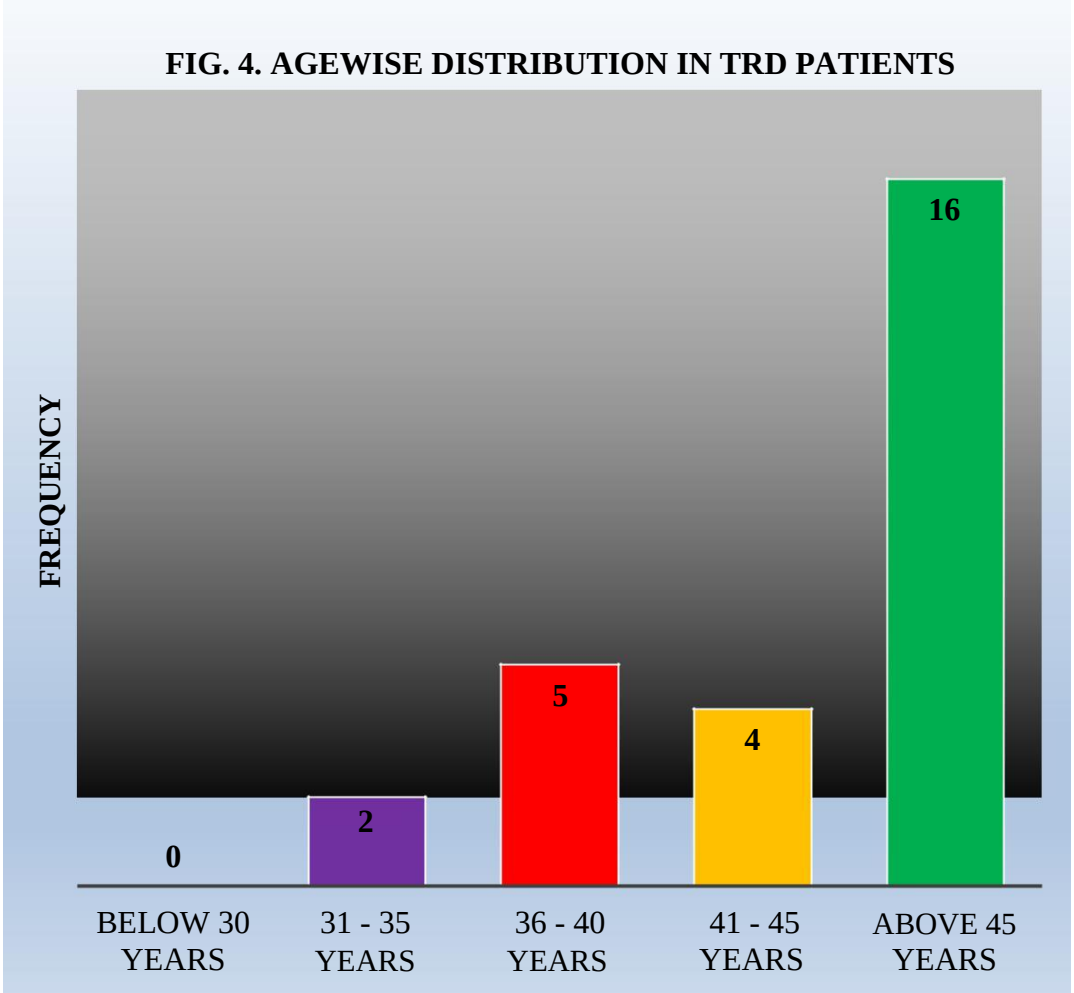
5.1.4 AGEWISE DISTRIBUTION OF THE PATIENTS IN PATIENTS WITH TREATMENT RESISTANT DEPRESSION:

The mean age =49 ± 10.7 years (Range- 31 to 65 years).

Age category: Below 30=0%, 31 to 35=7.4% (n=2), 36 to 40=18.5% (n=5), 41 to 45=14.8% (n=4) and above 45=59.3% (n=16).

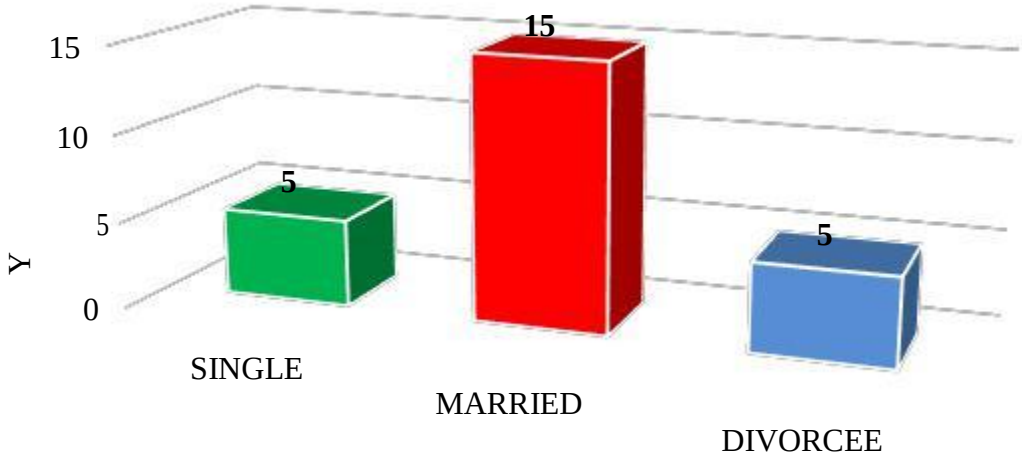
FIG. 4. AGEWISE DISTRIBUTION IN TRD PATIENTS



5.1.5 MARITAL STATUS IN PATIENTS WITH TREATMENT RESISTANT SCHIZOPHRENIA:

In this study, out of the 25 patients 15 patients (60%) were married, 5 patients (20%) were single and 5 patients (20%) were divorcee.

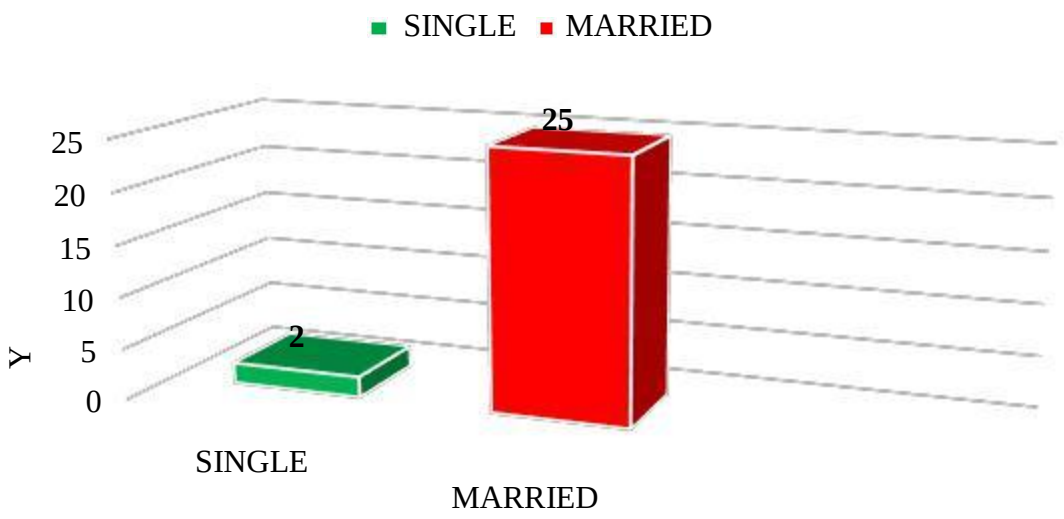
FIG. 5. MARITAL STATUS IN TRS PATIENTS



5.1.6 MARITAL STATUS IN PATIENTS WITH TREATMENT RESISTANT DEPRESSION:

In this study, out of 27 patients, 25 patients (92.6%) were married and 2 patients (7.4%) were single.

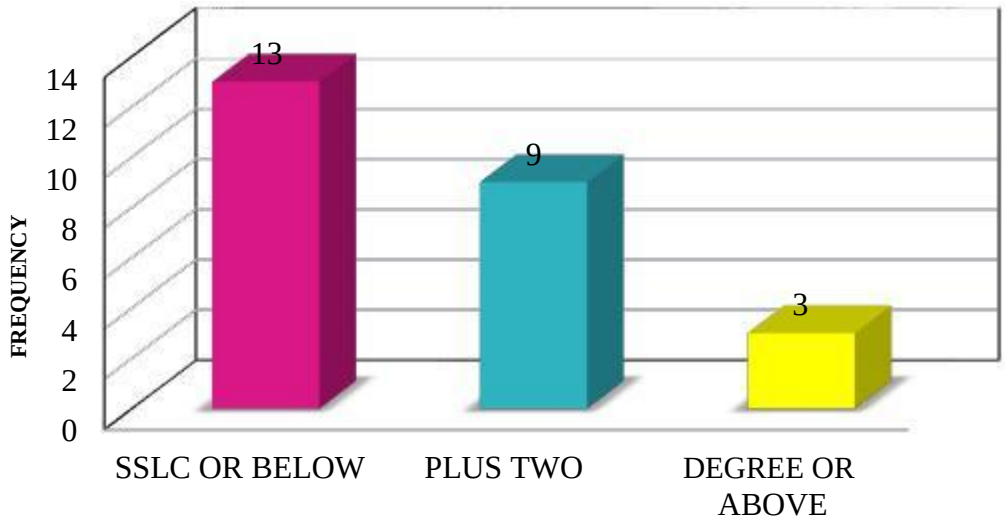
FIG. 6. MARITAL STATUS IN TRD PATIENTS



5.1.7 EDUCATIONAL QUALIFICATION IN PATIENTS WITH TREATMENT RESISTANT SCHIZOPHRENIA:

In this study, out of the 25 patients about 52.0% (n=13) had an education ≤SSLC, about 36% (n=9) had an education of plus two and about 12% (n= 3) had an education of degree or above.

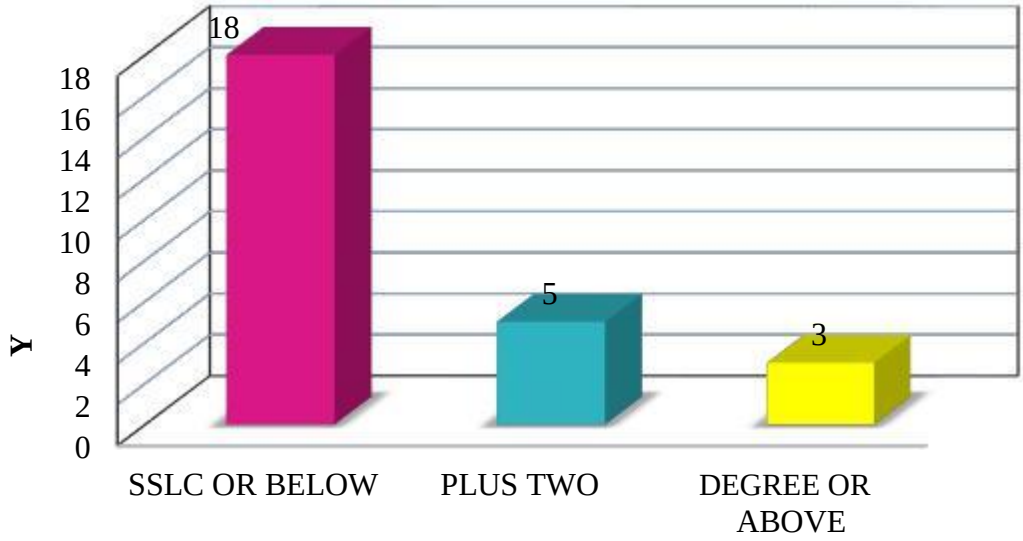
FIG. 7. EDUCATIONAL QUALIFICATION IN TRS PATIENTS



5.1.8 EDUCATIONAL QUALIFICATION IN PATIENTS WITH TREATMENT RESISTANT DEPRESSION:

In this study, about 66.7% (n=18) had an education ≤SSLC, about 18.5% (n=5) had an education of plus two and about 14.8% (n=4) had an education of degree or above.

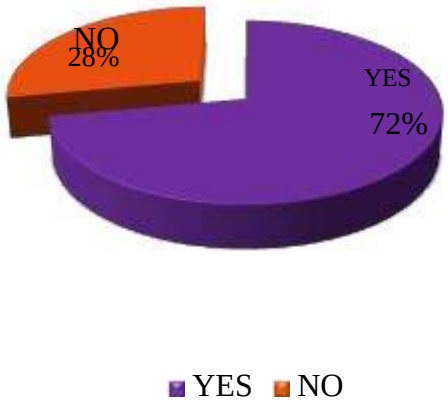
FIG. 8. EDUCATIONAL QUALIFICATION IN TRD PATIENTS



5.1.9 FAMILY HISTORY OF ANY PSYCHIATRIC CONDITIONS IN PATIENTS WITH TREATMENT RESISTANT SCHIZOPHRENIA:

Of the total 25 patients, about 72% (n=18) had a family history of any psychiatric conditions and 28% (n=7) had no family history.

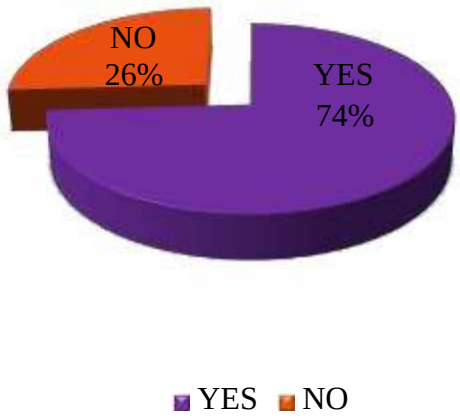
FIG. 9. FAMILY HISTORY OF ANY PSYCHIATRIC CONDITIONS IN TRS PATIENTS



5.1.10 FAMILY HISTORY OF ANY PSYCHIATRIC CONDITIONS IN PATIENTS WITH TREATMENT RESISTANT DEPRESSION:

Of the total 27 patients, about 74.1% (n=20) had a family history of any psychiatric conditions and 25.9% (n=7) had no family history.

FIG. 10. FAMILY HISTORY OF ANY PSYCHIATRIC CONDITIONS IN TRD PATIENTS



5.2 MANAGEMENT STRATEGIES

5.2.1 CHOICE OF THERAPY IN PATIENTS WITH TREATMENT RESISTANT SCHIZOPHRENIA:

Clozapine + Amisulpride combination (20%, n=5) was majorly used. Least consumption was Clozapine + Olanzapine + Amisulpride + Risperidone + Iloperidone combination and Clozapine + Haloperidol + Olanzapine + Risperidone combination (4%, n=1). Clozapine was given alone in one patient (4%).

TABLE NO. 1 CHOICE OF THERAPY IN TRS PATIENTS

S. No.	DRUGS	Frequency	Percent
1.	Clozapine + Amisulpride	5	20.0%
2.	Clozapine + Aripiprazole	4	16.0%
3.	Clozapine + Olanzapine + Amisulpride	3	12.0%
4.	Clozapine + Risperidone	3	12.0%
5.	Clozapine + Haloperidol + Olanzapine + ECT	3	12.0%
6.	Clozapine + Olanzapine + Risperidone	2	8.0%
7.	Clozapine + Olanzapine + Amisulpride + ECT + Risperidone	2	8.0%
8.	Clozapine + Olanzapine + Amisulpride + Risperidone + Iloperidone	1	4.0%
9.	Clozapine	1	4.0%
10.	Clozapine + Haloperidol + Olanzapine + Risperidone	1	4.0%

5.2.2 CHOICE OF THERAPY IN PATIENTS WITH TREATMENT RESISTANT DEPRESSION:

Sertraline + Venlafaxine + Sodium valproate (22.2%, n=6) was majorly used. Least consumption was Sertraline + Amitryptiline + Venlafaxine + Lithium + Sodium valproate combination and Sertraline + Venlafaxine + Bupropion + Lithium + Sodium valproate + ECT combination (3.7%, n=1).

TABLE NO. 2 CHOICE OF THERAPY IN TRD PATIENTS

S. No.	DRUGS	Frequency	Percent
1	Sertraline + Venlafaxine + Sodium valproate	6	22.2%
2	Sertraline + Venlafaxine + Escitalopram	4	14.8%
3	Venlafaxine + Sodium valproate + Escitalopram	3	11.1%
4	Venlafaxine + Lithium + Escitalopram	3	11.1%
5	Sertraline + Amitryptiline + Venlafaxine	3	11.1%
6	Venlafaxine + Lithium + Escitalopram + ECT	2	7.4%
7	Mirtazapine + Lithium + Sodium valproate	2	7.4%
8	Bupropion + Lithium + Sodium valproate + Escitalopram	2	7.4%
9	Sertraline + Amitryptiline + Venlafaxine + Lithium + Sodium valproate	1	3.7%
10	Sertraline + Venlafaxine + Bupropion + Lithium + Sodium valproate + ECT	1	3.7%

5.2.3 DOSE ANALYSIS IN PATIENTS WITH TREATMENT RESISTANT SCHIZOPHRENIA:

Clozapine 100 mg was the mostly used (n=13) dose in this study. Clozapine 50 mg dose was also used widely (n=9). Olanzapine 20 mg was also used in many patients (n=6). Haloperidol 5mg, 20 mg, Olanzapine 210 mg, Aripiprazole 10mg, 30mg and Iloperidone 12mg were used rarely.

TABLE NO. 3 DOSE ANALYSIS IN TRS PATIENTS

DRUG	DOSES GIVEN PER DAY	NUMBER OF PATIENTS TREATED
CLOZAPINE	25 mg	3
	50 mg	9
	100 mg	13
HALOPERIDOL	5 mg	1
	10 mg	2
	20 mg	1
AMISULPRIDE	10 mg	4
	20 mg	5
	50 mg	2
OLANZAPINE	7. 5 mg	3
	20 mg	6
	30 mg	2
	210 mg	1
RISPERIDONE	1 mg	3
	2 mg	3
	3 mg	3
ARIPIPRAZOLE	10 mg	1
	15 mg	2
	30 mg	1
ILOPERIDONE	12 mg	1

5.2.4 DOSE ANALYSIS IN PATIENTS WITH TREATMENT RESISTANT DEPRESSION:

Lithium 300 mg was widely used dose (n=11). Venlafaxine 150 mg was given in most of the TRD patients (n=8). Apart from 150 mg dose, venlafaxine was also given in 50 mg (n=6), 75 mg (n=4) and 225 mg doses (n=2). Amitriptyline 100 mg, 150 mg and Bupropion 150 mg were the least used doses.

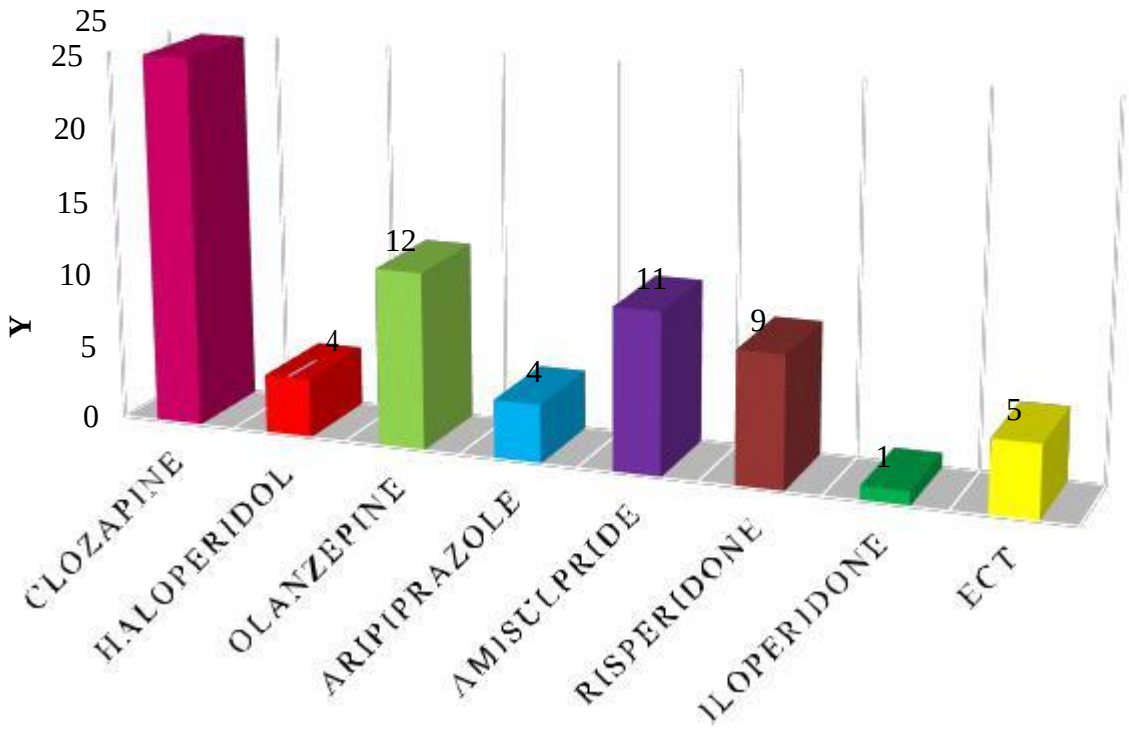
TABLE NO. 4 DOSE ANALYSIS IN TRD PATIENTS

DRUGS	DOSE GIVEN PER DAY	NO.OF PATIENTS TREATED
SERTRALINE	25 mg	3
	50 mg	5
	100 mg	7
VENLAFAXINE	50 mg	6
	75 mg	5
	150 mg	10
	225 mg	2
BUPROPION	100 mg	2
	150 mg	1
LITHIUM	300 mg	11
SODIUM VALPROATE	125 mg	5
	250 mg	6
	500 mg	4
MIRTAZAPINE	15 mg	2
ESCITALOPRAM	10 mg	6
	20 mg	5
	40 mg	3
AMITRIPTYLINE	100 mg	2
	150 mg	1
	200 mg	1

5.2.5 DRUG USE PATTERN IN PATIENTS WITH TREATMENT RESISTANT SCHIZOPHRENIA:

Clozapine was given to all the patients treated (100%, n=25). Amisulpride was given in 44% (n=11) of patients. Olanzapine was used in 48% (n=12) and risperidone was used in 36% (n= 9) of patients. ECT was given for 50% (n=5) of the total patients. Aripiprazole was used in 16% (n=4) of patients. Iloperidone was given only to one patient (4%).

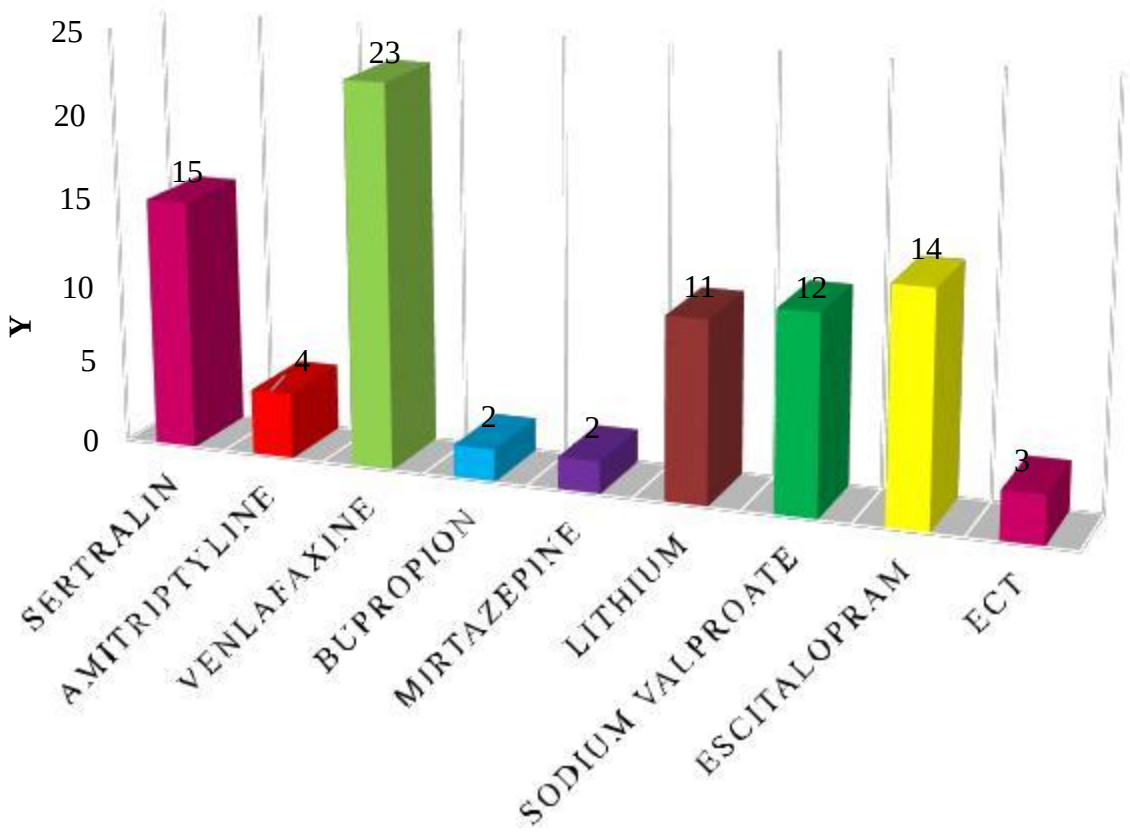
FIG. 11 DRUG USE PATTERN IN TRS PATIENTS



5.2.6 DRUG USE PATTERN IN PATIENTS WITH TREATMENT RESISTANT DEPRESSION:

Venlafaxine was given to 85.19% (n=23) of the patients. Sertraline was given in 55.6% (n=15) of patients and escitalopram was given in 51.85% (n=14) of patients. Sodium valproate was used in 44.4% (n=12) and lithium was used in 40.74% (n=11) of patients. Amitriptyline was used in 14.8% (n=4) of patients. ECT was given for 11.1% (n=3) and bupropion and mirtazapine was used in 7.4% (n=2) of patients.

FIG. 12 DRUG USE PATTERN IN TRD PATIENTS



5.3 SCORING OF SYMPTOMS

5.3.1 PANSS SCORING FOR PATIENTS WITH TREATMENT RESISTANT SCHIZOPHRENIA:

Initial PANSS score represents the severity of symptoms in treatment resistant schizophrenia before the treatment and final PANSS score represents the symptoms severity after treatment. Here initial PANSS score had a mean of 107.64 ± 30.89 and final PANSS score had a mean of 83.96 ± 25.33. The mean difference was 23.68. Wilcoxon Signed Ranks Test was used to test the significance and the study was significant with Z=4.378 and p=0.001 at 1% level of significance.

TABLE NO. 5 PANSS SCORE IN TRS PATIENTS

PANSS	Mean	SD	Mean difference	Wilcoxon Signed Ranks Test	
				Z	P value
INITIAL	107.64	30.89	23.68	4.378	0.001*
FINAL	83.96	25.33			

* Significant at 1% level of significance

5.3.2 MADRS SCORING FOR PATIENTS WITH TREATMENT RESISTANT DEPRESSION:

Initial MADRS score represents the severity of symptoms in treatment resistant depression before the treatment and final MADRS score represents the symptoms severity after treatment. Here initial MADRS score had a mean of 40.11 ± 6.16 and final MADRS score had a mean of 24.85 ± 3.32. The mean difference was 15.26. Wilcoxon Signed Ranks Test was used to test the significance and the study was significant with Z=4.557 and p=0.001 at 1% level of significance.

TABLE NO.6 MADRSS SCORE IN TRD PATIENTS

MADRS	Mean	SD	Mean difference	Wilcoxon Signed Ranks Test	
				Z	P value
INITIAL	40.11	6.16	15.26	4.557	0.001*
FINAL	24.85	3.32			

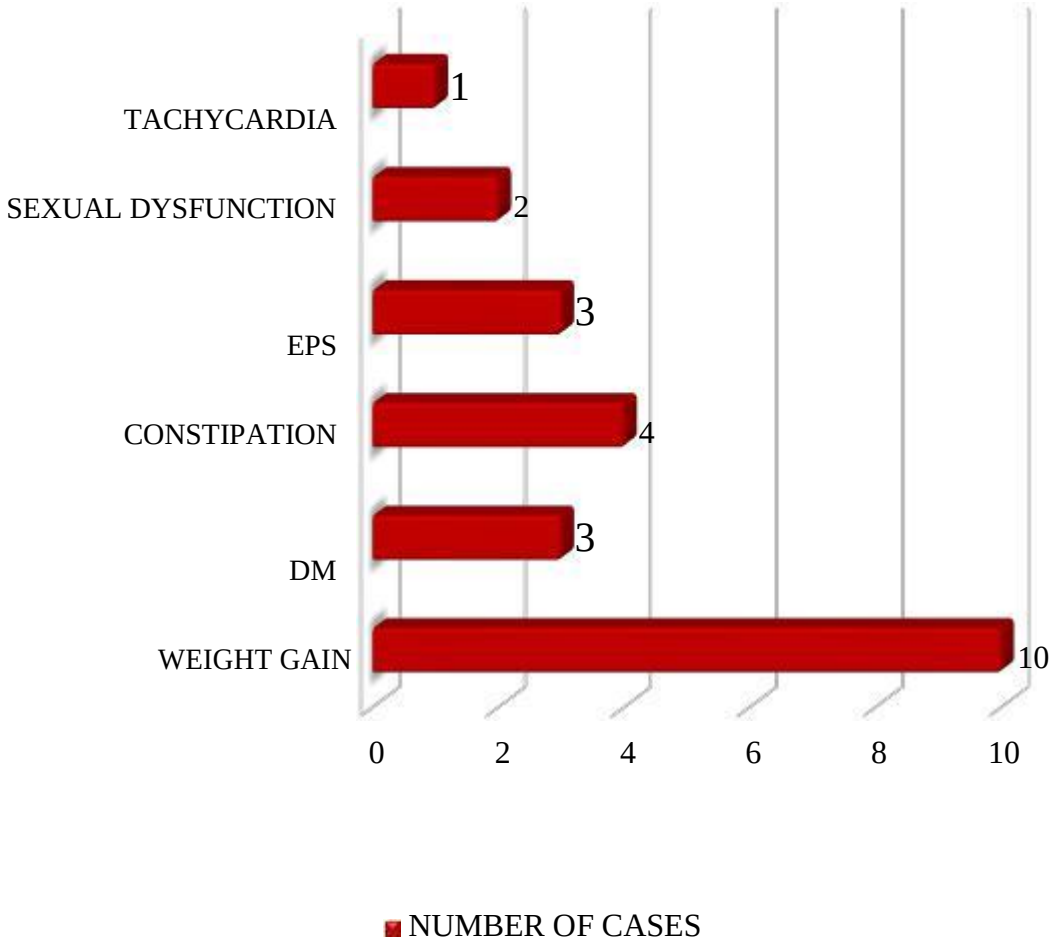
* Significant at 1% level of significance

5.4. ADR REPORTING

5.4.1 ADRs OBSERVED IN PATIENTS WITH TREATMENT RESISTANT SCHIZOPHRENIA:

Weight gain (n=10), constipation (n=4), EPS (n=3), DM (n=3), sexual dysfunction (n=2) and tachycardia (n=1) were the observed ADRs in the 25 patients during the study period.

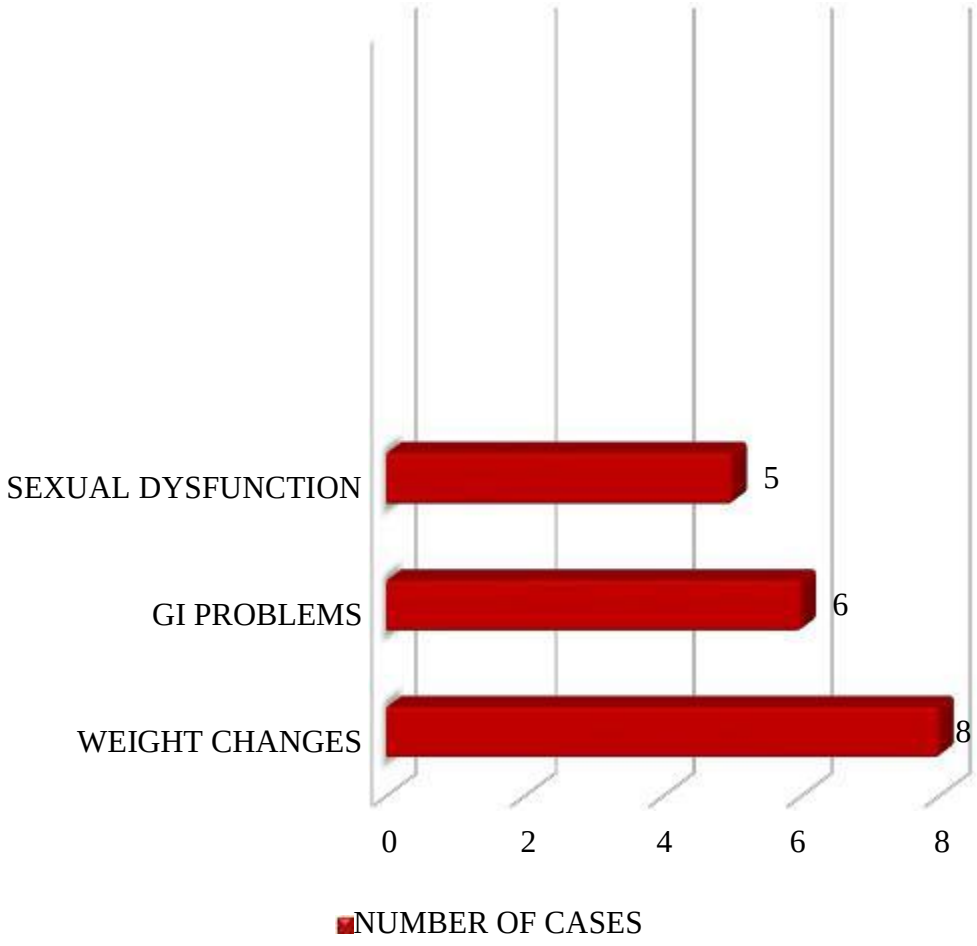
FIG. 11. ADRs OBSERVED IN TRS PATIENTS



5.4.2 ADRs OBSERVED IN PATIENTS WITH TREATMENT RESISTANT DEPRESSION:

Weight changes (n=8), sexual dysfunction (n=5) and GI problems (n=6) were the observed ADRs in the 27 patients during the study period.

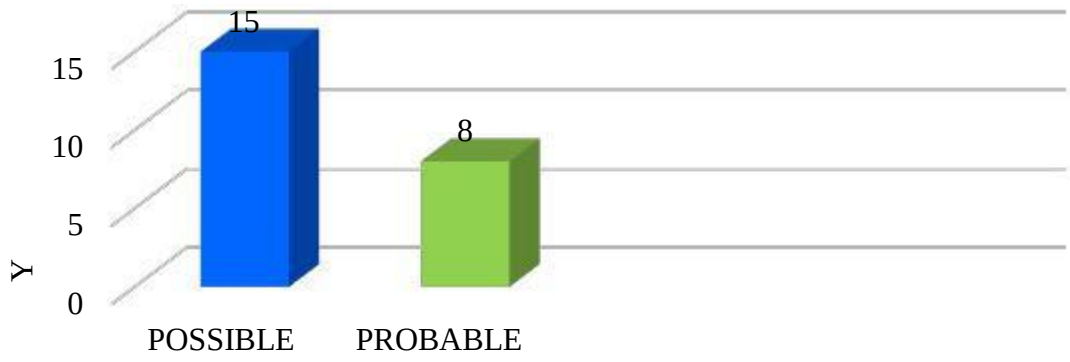
FIG. 12. ADRs OBSERVED IN TRD PATIENTS



5.4.3 CAUSALITY OF ADR IN PATIENTS WITH TREATMENT RESISTANT SCHIZOPHRENIA:

When analysed on Naranjo ADR probability scale, majority of ADRs were rated as possible [n = 15 (65.22%)], followed by probable [n =8 (34.78%)].

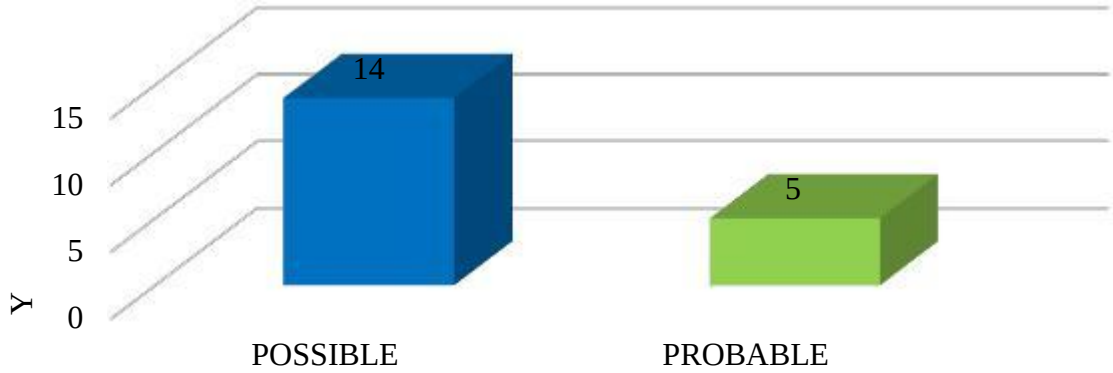
FIG. 13 CAUSALITY OF ADR IN TRS PATIENTS



5.4.4 CAUSALITY OF ADR IN PATIENTS WITH TREATMENT RESISTANT DEPRESSION:

When analysed on Naranjo ADR probability scale, majority of ADRs were rated as possible [n = 14 (73.68%)], followed by probable [n = 5 (26. 32%)].

FIG. 14 CAUSALITY OF ADR IN TRD PATIENTS



DISCUSSION

6. DISCUSSION

Management of treatment resistant conditions of schizophrenia and depression were analyzed in the study. Evaluation and updating of the knowledge on these conditions and the therapies help clinicians in their effective patient care. The result of this study may be helpful for clinicians to provide an insight to treatment modalities given in our hospital setting and thereby improve their clinical perspective in this area. It is also very helpful for health system decision makers to reduce the incidence of adverse drug reactions and thereby the patient sufferings and cost of therapy. Understanding the demographic profile of the TRS and TRD patients will help healthcare practitioners better prepare for the problems caused by the world's rapidly expanding population. The importance of demography lies in its contribution to helping government and society better prepare to deal for the issues and demands of population growth, aging etc. Treatment resistant schizophrenia and treatment resistant depression are two major clinical challenges faced globally. Our study investigated the demographic profile and management strategies of the above mentioned conditions in our hospital setting.

Genderwise distribution of treatment resistant schizophrenia was assessed here. The results of the study evince that distribution in males were 52 % and in females were 48 % out of the 25 patients showing a small male predominance over female. *Uriel Heresco-Levy et al* [27] study reveals a same level of gender distribution in treatment resistant schizophrenic patients. Genderwise distribution of treatment resistant depression was also studied. There was 44.4% of males and 55.6 % females out of the total 27 patients who enrolled in the study. Here there was a female predominance over males. *Yiru Fang et al* [28] showed a 54% female supremacy in their study.

Through the study, it was perceived that mean age of treatment resistant schizophrenia to be =37.12 ± 7.79 years (Range: 26-57). Age category was ≤ 25=0%, 26 to 30=24%, 31 to 35=20%, 36 to 40=28%, 41 – 45 =16% and above 45 =12%. *Antonio T Lopes* et al [29] in their study showed a mean age of 43 ± 12 years (Range: 24-72) for treatment resistant schizophrenia. For treatment resistant depression, the mean age was = 49 ±

10.7 yrs., (Range- 31 to 65 yrs.). The age category was ≤ 30=0%, 31 to 35=7.4% (n=2), 36 to 40=18.5% (n=5), 41 to 45=14.8% (n=4) and above 45=59.3% (n=16). *Yiru Fang et al* [28] showed a mean age of 40.5 ± 11.5 years in their study for treatment resistant depression.

Marital status of the patients were evaluated. We found out that in treatment resistant schizophrenia out of 25 patients, 15 patients were married (60%), 5 patients were single (20%) and 5 patients were divorcee (20%). *Uriel Heresco-Levy et al* [30] study showed 73.4% patients (n=22) who are single which is contradictory to our study findings. Marital status of treatment resistant depression was also evaluated. Of the total 27 patients, 25 patients (92.6) were married and 2 patients (7.4%) were single. *Yiru Fang et al* [28] study shows a 70% patients who were married.

The evaluation of educational status in treatment resistant schizophrenia was made in the study. About 52.0% (n=13) had an education ≤SSLC, about 36% (n=9) had an education of plus two and about 12% (n= 3) had an education of degree or above out of the total sample in TRS. Most of the patients had an educational level of SSLC or less. *Theresa Wimberley et al* [31] in their study suggested the primary education level as 88% in treatment resistant schizophrenic patients. For treatment resistant depression, about 66.7% (n=18) had an education ≤SSLC, about 18.5% (n=5) had an education of plus two and about 14.8% (n=4) had an education of degree or above. Here also more patients had an educational qualification of SSLC or below. But the result was conflicting to the result of *M A Kenny et al* [32] study which suggest that 60% of patients had an educational qualification of degree or above.

Family history of any psychiatric conditions in patients with treatment resistant schizophrenia was assessed and out of the total 25 patients, about 72% (n=18) had a family history of any psychiatric conditions and 28% (n=7) had no family history. *Uriel Heresco-Levy et al* [30] showed a family history of mental illness in about 60% of the total patients. In treatment resistant depression, out of the total 27 patients, about 74.1% (n=20) had a family history of any psychiatric conditions and 25.9% (n=7) had

no family history. *Yiru Fang et al* [28] in their study showed a family history of any psychiatric illness was 100% in patients with treatment resistant depression.

Management of treatment resistant schizophrenia usually depends on the patient condition and the knowledge of treating physician. In our study, clozapine was found to be the widely used drug in our hospital setting (100%). All the patients who had TRS was treated with clozapine with different doses and showed improvement in PANSS scores. *R. K. Solanki et al* [33] suggest that clozapine emerges to be the gold standard in TRS patients. The most consisting results regarding efficacy in their study group had been observed with clozapine. The data from studies showed superior effects of clozapine on positive and negative symptoms, compared to prior treatment with typical neuroleptics.

Clozapine + amisulpride combination was used in 20% of the patients and was the mostly used combination. The patients also showed improvement in their PANSS score after the treatment. A case series by *Zink et al* [34] showed improvement in previously treatment resistant symptoms following a combined treatment strategy of clozapine and amisulpride. *Rob Kerwin et al* [26] performed an open trial of amisulpride augmentation in a long term (52 weeks) study. Significant improvement was observed in most of the patients with no additional side effects. Clozapine + aripiprazole combination was used in 16% of the patients with TRS and an improvement in the psychotic symptoms were observed in them. *Nilufar Mossaheb et al* [35], in their study showed that using aripiprazole augmentation in treatment resistant schizophrenia with clozapine effectively reduced the symptoms in most of the patients.

Augmentation therapy of clozapine with other antipsychotics such as risperidone, olanzapine, haloperidol and iloperidone were given for many patients with TRS and showed significant improvement in their symptoms. *R K Solanki et al* [33] showed the effectiveness of using first generation and second generation antipsychotics in combination with clozapine in their study. *Miranda Chakos et al* [36] revealed the results of a meta-analysis indicating that clozapine augmentation with atypical and typical antipsychotics improve the symptoms of treatment resistant schizophrenia in majority of the studied cases. Electro convulsive therapy was given as augmentation with clozapine and other antipsychotics in many patients (20%) and shown

improvement in their symptoms. *Levy-Rueff et al* [37] in their study implicated the improvement in symptoms when ECT was given along with antipsychotics.

Treatment resistant depression was also managed with augmentation strategies in our hospital setting. Sertraline + venlafaxine + sodium valproate combination was majorly used in treating TRD patients (22.2%). *Vieta E et al* [38] in their research study suggested the effectiveness of using sertraline along with venlafaxine and sodium valproate in treatment resistant depression and their lower incidence of side effects. *Martin Lopez et al* [39] also established the effectiveness of using the above combination in TRD patients in their study. Venlafaxine was the drug used in majority (85.19%) of the TRD patients and it improved the symptoms in them. There were reduction in the MADRS score showing their improvement. *Nierenburg et al* [40] reported an improvement in response rate of 40% in patients treated with venlafaxine who had failed a minimum of three adequate antidepressant trials.

Lithium was also used in many patients (40.7%) as an augmentation therapy with other antidepressants. It also helped to improve the MADRS score in TRD patients. *Fava M et al* [41] in the well-studied and most established meta-analysis found 52% response rate in lithium treated TRD patients showing its use as an augmentation therapy in these patients. Sertraline (55.6%) and escitalopram (51.8%) were also used in the management of TRD in the hospital. *Khalid Saad Al-Harbi* [11] in his meta-analysis explained the use of sertraline and escitalopram along with venlafaxine and lithium in the management of symptoms in TRD patients. Use of sertraline and escitalopram improved the MADRS score in the treated patients.

Bupropion, mirtazapine, sodium valproate and amitriptyline were also used as augmentation with venlafaxine and SSRIs in many patients. The combined use of these drugs improved the mental condition in most patients. *Bodkin JA et al* [42] examined combining bupropion and an SSRI or bupropion and venlafaxine and the response rate were more than 75% in the study. *Carpenter LL et al* [43] in an open labelled study in TRD patients, mirtazapine showed a response rate of 55% in nonresponders to standard antidepressants. *Coraddo Barbui et al* [44] in a systematic review of various RCTs of amitriptyline and SSRIs showed a 2.5% difference in the proportion of responders in favor of amitriptyline. ECT was also given in 11.1% of the TRD patients along with

other augmentation therapies. There were significant control over symptoms in most of the patients. *Thase ME et al* [45] in their study reported a response rate of 50% to 89% in patients who failed to respond to a single antidepressant.

Initial PANSS score represents the severity of symptoms in treatment resistant schizophrenia before the treatment and final PANSS score represents the symptoms severity after treatment. In this study, initial PANSS score had a mean of 107.64 ± 30.89 and final PANSS score had a mean of 83.96 ± 25.33. The mean difference was 23.68. Wilcoxon Signed Ranks Test was used to test the significance and the study was significant with Z=4.378 and p=0.001 at 1% level of significance. The significance of the PANSS score difference suggested the effectiveness of treatment given. Large scale studies shows the significant reduction in TRS symptoms and effectiveness of treatment when PANSS initial and final scores differ significantly.

Initial MADRS score represents the severity of symptoms in treatment resistant depression before the treatment and final MADRS score represents the symptoms severity after treatment. Here initial MADRS score had a mean of 40.11 ± 6.16 and final MADRS score had a mean of 24.85 ± 3.32. The mean difference was 15.26. Wilcoxon Signed Ranks Test was used to test the significance and the study was significant with Z=4.557 and p=0.001 at 1% level of significance. The significance of the MADRS score difference suggested the effectiveness of treatment given. Large scale studies shows the significant reduction in TRD symptoms and effectiveness of treatment when MADRS initial and final scores differ significantly.

The adverse drug reactions that occurred in the patients during the study were evaluated and causality assessment were done using Naranjos scale. Out of the 25 patients, 40% had an ADR of weight gain (n=10), 16% had the incidence of constipation (n=4), 12% had the episodes of EPS (n=3), 12% had incidence of DM (n=3), 8 had an ADR of sexual dysfunction (n=2) and 4% had tachycardia (n=1) during the study period. *Krakowski M et al* [46] in their study showed the incidence of weight gain and increased glucose level in patients who were taking clozapine and other second generation antipsychotics. *Nilufar Mossaheb et al* [35] in their study on aripiprazole established the occurrence of side effects like EPS and constipation in the study subjects. *J Bobes et al* [47] studied the frequency of sexual dysfunction in patients

using risperidone, olanzapine and haloperidol and found out high frequency of sexual dysfunction with these drugs. *Kupchik et al* [48] in their recent study about clozapine with ECT found out the occurrence of supraventricular and sinus tachycardia in some patients. When analysed on Naranjo ADR probability scale, majority of ADRs were rated as possible [n = 15 (65.22%)], followed by probable [n =8 (34.78%)].

Out of the total 27 TRD patients, 29.6% experienced an ADR of weight changes (n=8), 18.52% experienced sexual dysfunction (n=5) and 22.22% experienced GI problems (n=6) during the study period. *Yiru Fang et al* [28] in their study about venlafaxine and mirtazapine shows the incidence of weight changes in patients with TRD as adverse drug effect. This study also gives evidences for the occurrence of GI disturbances in patients taking venlafaxine and mirtazapine. *Montejo et al* [49] reveals the incidence of sexual dysfunctions in patients taking venlafaxine, SSRIs etc in a prospective multicenter study. When analyzed on Naranjo ADR probability scale, majority of ADRs were rated as possible [n = 14 (73.68%)], followed by probable [n = 5 (26. 32%)].

CONCLUSION

7. CONCLUSION

Treatment resistance in psychiatric patients is the major clinical challenge faced globally. Treatment resistance is generally defined as inadequate responses to a succession of treatments. The observations of the current study demonstrated the demographic profile and management strategies of treatment resistant schizophrenia and treatment resistant depression. An astronomical degree of treatment resistance was shown by many patients in the psychiatric department of our hospital.

TRS and TRD are the major clinical challenges faced by the psychiatrists in the aspect of pharmacological management of these disorders. The major approach lies in providing a greater impact on quality of life of these patients. This study focused on the therapeutic options in case of treatment resistance which is clinically significant. Thus the study offered greater benefit to these patients by optimizing the treatment strategy and proper monitoring of adverse drug event of the drug. Moreover no study had been conducted so far in this area in the topic chosen in the particular demographic group. Therefore this study was conducted in these patients with treatment resistant schizophrenia and treatment resistant depression in a tertiary care referral hospital

From the evaluation of the demographic profile, it concluded that the gender doesn't have much influence on the occurrence of TRS. But in cases of TRD, females had predominance over males. Furthermore family history had a strong correlation with the occurrence of both TRD and TRS.

In some cases it was impossible to control the symptoms of both TRS and TRD and it is the biggest issue faced by physicians treating patients who were resistant to therapy. In psychiatric department of the hospital, clozapine is widely used to treat TRS patients in different doses along with other antipsychotic drugs. After the course of therapy, the patient's PANSS scores shown improvement. TRD, a complex clinical problem caused by multiple risk factors, was targeted by integrated therapeutic strategies which include optimization of medications, a combination of anti-depressants, switching of anti-

depressants, and an augmentation with non-antidepressants, psychosocial and cultural therapies and somatic therapies including ECT etc.

Sertraline, Venlafaxine and Sodium valproate combination was majorly used in the treatment of TRD patients. Among them, Venlafaxine was used commonly in TRD. And the MADRS scores shown improvement in patient condition. Apart from drug therapy ECT when given in combination with antipsychotics were also effective in both TRS and TRD.

Any unintended or noxious reaction up on the intake of the drug can be termed as adverse drug reactions. Psychiatric drugs are known to cause many adverse effects such as extra pyramidal symptoms, metabolic syndrome, hormonal issues etc. In this study the major ADRs shown by TRS patients include weight gain, constipation, diabetes mellitus, extra pyramidal symptoms, sexual dysfunction and tachycardia and those of TRD patients include weight changes, GI problems and sexual dysfunction.

During the study, many challenges and limitations were faced due to its complexity in its nature. Ethical issues, fluctuations in illness, study patients run the risk of worsening of illness and suicide risk as well as the non-adherence to treatment and not appearing on OPD regularly for follow up. Rating scales are essential for assessment of drug response, but those were not suitable for all patients especially those with a poor socioeconomic status.

In summary, TRS in this specific population unresponsive to previous treatment, a combination of clozapine with aripiprazole, as well as other augmentation strategies for clozapine, seen worthy of further exploration. However, given the lack of clear cut evidence for an advantage of antipsychotic poly pharmacy in general, no confident recommendations can be made and careful clinical appraisal of the risk benefit ratio of all options is warranted.

TRD continued to challenge mental health care providers and further relevant research involving newer drugs is warranted to improve the quality of life of patients with the disorder. And some groups of patient needs further study to identify the most effective therapeutic modalities. Newer biomarker based anti-depressants and other drugs

together with non-drug strategies, are on the horizon to address further the multiple complex issues of treatment resistant depression.

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9. BIBLIOGRAPHIC REFERENCES

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ANNEXURE

ANNEXURE I

DATA COLLECTION FORM

DEMOGRAPHIC PROFILE AND MANAGEMENT STRATEGIES OF TREATMENT RESISTANT SCHIZOPHRENIA AND TREATMENT RESISTANT DEPRESSION IN A TERTIARY CARE REFERRAL HOSPITAL

DATA COLLECTION FORM

Case no :		Date : / /

Patient demographic details

Name :	Mrd No :	Age when treatment started:	Age at which treatment resistance diagnosed:
Sex :	DOA :	DOD :	
Weight :	Marital status :	Education :	
Occupation :	Religion:	Others:	

Presenting symptoms

Date of symptom onset: Date of first presentation for medical care:

Patient history

History of illness

Medical history

□ DM □ Asthma □ Arthritis
□ HTN □ Cardiovascular disease □ COPD
□ Renal disease □ Liver diseases
If others (please specify):

Medication history

Family history of psychiatric disorders
General relatives:
Degree of relatives:
Relatives with treatment resistance:

Personal habits: Alcohol □ Tobacco □ Others:

Food habits: Vegetarian □ Non vegetarian □

Drug allergy:

Others if any specify:

Patient level of social function evaluation:

Psychotherapy

Drugs	Duration	When started after onset of disease

Drug	Dose	Class	Duration	Switch Off	Percentage of dose increment

Scoring as per scale:

Comment on therapy:

Cognitive behaviour therapy (CBT):

Electroconvulsive therapy (ECT):

Number	Duration	Current given	Duration of seizure

Lab reports:

Test	Patient value								Normal value
	1st visit	2nd visit	3rd visit	4th visit	5th visit	6th visit	7th visit	8th visit	

Adverse drug reactions (ADR)

Type of ADR	Description	Causative drug	Naranjo scale score	Duration of intake of drug	Management strategy

ANNEXURE IV

INFORMED CONSENT (ENGLISH)

DEMOGRAPHIC PROFILE AND MANAGEMENT STRATEGIES OF TREATMENT RESISTANT SCHIZOPHRENIA AND TREATMENT RESISTANT DEPRESSION IN A TERTIARY CARE REFERRAL HOSPITAL

PATIENT CONSENT FORM

The department of Pharmacy Practice of Al-Shifa College of Pharmacy in association with department of Psychiatry at KIMS-AlShifa Hospital supports the practice of protection of human participants in research. The following will provide you with information about study that will help you in deciding whether or not you wish to participate. If you agree to participate, please be aware that you are free to withdraw at any point throughout the duration of study.

In this study medical records of the patient will be used to assess the demographic profile and to evaluate the management strategies of treatment resistant schizophrenia or treatment resistant depression. All information provided will remain confidential and will not be associated with the patient name. You will be free to ask any questions and will be provided with the results of the study if you request them. If you have any further question concerning the study please feel free to contact us through phone (9496646355) or email (fifthyearproject2016@gmail.com).

Please indicate with your signature on the space below that you understand your rights and agree to participate in the study. All information will be kept confidential and patient name will not be associated with any research findings when publishing the study report.

NAME OF PERSON GIVING CONSENT:

SIGNATURE:

RELATION WITH THE PARTICIPANT:

DATE:

PLACE:

ANNEXURE V

INFORMED CONSENT (MALAYALAM)

DEMOGRAPHIC PROFILE AND MANAGEMENT STRATEGIES OF TREATMENT RESISTANT SCHIZOPHRENIA AND TREATMENT RESISTANT DEPRESSION IN A TERTIARY CARE REFERRAL HOSPITAL

രോഗിയുടെ സമ്മതപത്രം

അൽഷിഫ ഫാർമസി കോളേജിലെ ഫാർമസി പ്രാക്ടീസ് വിഭാഗവും കിംസ് അൽഷിഫ ആശുപത്രിയിലെ മാനസികാരോഗ്യ വിഭാഗവും ചേർന്നു നടത്തുന്ന പഠനത്തിൽ പങ്കെടുക്കുന്ന വ്യക്തിയുടെ അവകാശം ഉറപ്പു വരുത്തുവാൻ ഞങ്ങൾ ആഗ്രഹിക്കുന്നു. താഴെ പറയുന്ന കാര്യങ്ങൾ ഈ പഠനത്തെ കുറിച്ചും ഇതിൽ പങ്കെടുക്കുന്നതിന്റെ ആവശ്യകതയെ കുറിച്ചും പറയുന്നു. ഈ പഠനത്തിൽ താങ്കൾക്കു സ്വമേധയ പങ്കെടുക്കാം. എപ്പോൾ വേണമെങ്കിലും ഇതിൽ നിന്നും പിന്മാറാൻ താങ്കൾ സ്വതന്ത്രനാണ്.

ഈ പഠനത്തിൽ ചികിത്സാ പ്രതിരോധ ചിത്തഭ്രമം അല്ലെങ്കിൽ ചികിത്സാ പ്രതിരോധ വിഷാദരോഗം എന്നിവയുടെ ചികിത്സാരീതിയും വ്യക്തിഗത വിവരങ്ങളും മനസിലാക്കുവാൻ രോഗിയുടെ ചികിത്സാ രേഖകൾ ഉപയോഗപ്പെടുത്തുന്നു. ഇതിൽ നിന്നും ലഭിക്കുന്ന വിവരങ്ങൾ രഹസ്യമായിരിക്കുമെന്ന് ഇതിനാൽ ഞങ്ങൾ ഉറപ്പുതരുന്നു. ഈ പഠനത്തെ കുറിച്ചോ ഇതിനിടെ ഉണ്ടാകുന്ന കുറിച്ചോ എപ്പോൾ വേണമെങ്കിലും താങ്കൾക്ക് ഫോൺ(9496646355) വഴിയോ ഇമെയിൽ (fifthyearproject2016@gmail.com) വഴിയോ ചോദിച്ചറിയാം.

താങ്കൾക്ക് ഈ പഠനത്തിൽ പങ്കെടുക്കുവാൻ സമ്മതം ആണെങ്കിൽ താഴെ പറഞ്ഞിരിക്കുന്ന മാതൃകയിൽ പേരെഴുതി ഒപ്പ് നൽകി സഹകരിക്കേണ്ടതാണ്. താങ്കളുടെ പേരും നൽകുന്ന മറ്റു വിവരങ്ങളും ഈ പഠനം പ്രസിദ്ധീകരിക്കുകയാണെങ്കിലും രഹസ്യമായി തന്നെ സൂക്ഷിക്കുന്നതായിരിക്കും.

സമ്മതം നൽകുന്ന വ്യക്തിയുടെ പേര്:

ഒപ്പ്:

രോഗിയുമായുള്ള ബന്ധം:

തീയ്യതി:

സാക്ഷി:

ANNEXURE VI
POSITIVE AND NEGATIVE SYNDROME SCALE

POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS)

Patient Information									
Patient		Date	Day	Mth.	Year	Time	Hour	Min	
Personal notes									

Scoring Procedure

Tick appropriate box for each item

P1. Delusions Beliefs which are unfounded, unrealistic, and idiosyncratic. Basis for rating thought content expressed in the interview and its influence on social relations and behavior.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Presence of one or two delusions which are vague, uncrystallized, and not tenaciously held. Delusions do not interfere with thinking, social relations, or behavior.	☐
4 Moderate - Presence of either a kaleidoscopic array of poorly formed, unstable delusions or of a few wellformed delusions that occasionally interfere with thinking, social relations, or behavior.	☐
5 Moderate severe - Presence of numerous well-formed delusions that are tenaciously held and occasionally interfere with thinking, social relations, or behavior.	☐
6 Severe - Presence of a stable set of delusions which are crystallized, possibly systematized, tenaciously held, and clearly interfere with thinking, social relations, and behavior.	☐
7 Extreme - Presence of a stable set of delusions which are either highly systematized or very numerous, and which dominate major facets of the patient's life. This frequently results in inappropriate and irresponsible action, which may even jeopardize the safety of the patient or others.	☐

P2. Conceptual disorganization Disorganized process of thinking characterized by disruption of goal-directed sequencing, e.g., circumstantiality, tangentiality, loose associations non sequiturs, gross illogicality, or thought block. Basis for rating: cognitive-verbal processes observed during the course of interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Thinking is circumstantial, tangential, or paralogical. There is some difficulty in directina thoughts toward a goal and some loosening o7 associations may be evidenced under pressure.	☐
4 Moderate - Able to focus thoughts when communications are brief and structured, but becomes loose or irrelevant when dealing with more complex communications or when under minimal pressure.	☐
5 Moderate severe - Generally has difficulty in organizing thoughts, as evidenced by frequent irrelevances, disconnectedness. or loosening of associations even when not under pressure.	☐
6 Severe - Thinking is seriously derailed and internally inconsistent, resulting in gross irrelevancies and disruption of thought processes, which occur almost constantly.	☐
7 Extreme - Thoughts are disrupted to the point where the patient is incoherent. There is marked loosening of associations, which results in total failure of communication, e.g., "word salad. or mutism.	☐

P3. Hallucinatory behavior Verbal report or behavior indicating perceptions which are not generated by external stimuli. These may occur in the auditory visual, olfactory, or somatic realms. Basis for rating: Verbal report and physical manifestations during the course of interview as well as reports of behavior by primary care workers or family.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - One or two clearly formed but infrequent hallucinations, or else a number of vaque abnormal perceptions which do not result in distortions of thinking or behavior.	☐
4 Moderate - Hallucinations occur frequently but not continuously, and the patient's thinking and behavior are affected only to a minor extent.	☐
5 Moderate severe - Hallucinations are frequent, may involve more than one sensory modality, and tend to distort thinking and/or disrupt behavior. Patient may have a delusional interpretation of these experiences and respond to them emotionally and, on occasion, verbally as well.	☐
6 Severe - Hallucinations are present almost continuously, causing major disruption of thinking and behavior. Patient treats these as real perceptions, and functioning is impeded by frequent emotional and verbal responses to them.	☐
7 Extreme - Patient is almost totally preoccupied with hallucinations, which virtually dominate thinking and behavior. Hallucinations are provided a rigid delusional interpretation and provoke verbal and behavioral responses, including obedience to command hallucinations.	☐

P4. Excitement Hyperactivity as reflected in accelerated motor behavior, heightened responsivity to stimuli hypervigilance, or excessive mood lability. Basis for rating: Behavioral manifestations during the course of interview as well as reports of behavior by primary care workers or family.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Tends to be slightly agitated, hypervigilant, or mildly overaroused throughout the interview, but without distinct episodes of excitement or marked moolabitity. Speech may be slightly pressured.	☐
4 Moderate - Agitation or overarousal is clearly evident throughout the interview, affecting speech and general mobility, or episodic outbursts occur sporadically	☐
5 Moderate severe - Significant hyperactivity or frequent outbursts of motor activity are observed, making it difficult for the patient to sit still for longer than several minutes at any given time.	☐
6 Severe - Marked excitement dominates the interview delimits attention, and to some extent affects personal functions such as eating and sleeping.	☐
7 Extreme - Marked excitement seriously interferes in eating and sleeping and makes interpersonal interactions virtually impossible. Acceleration of speech and motor activity may result in incoherence and exhaustion.	☐

P5. Grandiosity Exaggerated self-opinion and unrealistic convictions of superiority, including delusions of extraordinary abilities, wealth, knowledge, fame, power, and moral righteousness. Basis for rating: thought content expressed in the interview and its influence on behavior.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Some expansiveness or boastfulness is evident, but without clear-cut grandiose delusions.	☐
4 Moderate - Feels distinctly and unrealistically superior to others. Some poorly formed delusions about special status or abilities may be present but are not acted upon.	☐
5 Moderate severe - Clear-cut delusions concerning remarkable abilities, status, or power are expressed and influence attitude but not behavior.	☐
6 Severe - Clear-cut delusions of remarkable superiority involving more than one parameter (wealth, knowledge, fame, etc.) are expressed, notably influence interactions, and may be acted upon.	☐
7 Extreme - Thinking, interactions, and behavior are dominated by multiple delusions of amazing ability, wealth knowledge, fame, power, and/or moral stature; which may take on a bizarre quality.	☐

P6. Suspiciousness/persecution Unrealistic or exaggerated ideas of persecution, as reflected in guardedness, a distrustful attitude, suspicious hypervigilance, or frank delusions that others mean one harm. Basis for rating: thought content expressed in the interview and its influence on behavior.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Presents a guarded or even openly distrustful attitude, but thoughts, interactions, and behavior are minimally affected.	☐
4 Moderate - Distrustfulness is clearly evident and intrudes on the interview and/or behavoir, but there is no evidence of persecutory delusions. Alternatively, there may be indication of loosely formed persecutory delusions, but these do not seem to affect the patient's attitude or interpersonal relations	☐
5 Moderate severe - Patient shows marked distrust fulness, leading to major disruption of interpersonal relations, or else there are clear-cut persecutory delusions that have limited impact on interpersonal relations and behavoir.	☐
6 Severe - Clear-cut pervasive delusions of persecution which may be systematized and significantly interfere in interpersonal relations.	☐
7 Extreme - A network of systematized persecutory delusions dominates the patient's thinking, social relations, and behavior.	☐

P7. Hostility Verbal and nonverbal expressions of anger and resentment, including sarcasm, passive-aggressive behavior, verbal abuse, and assaultiveness. Basis for rating: interpersonal behavoir observed during the interview and reports by primary care workers or family.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Indirect or restrained communication of anger such as sarcasm, disrespect, hostile expressions, and occasional irritability.	☐
4 Moderate - Presents an overtly hostile attitude, showing frequent irritability and direct expression of anger or resentment.	☐
5 Moderate severe - Patient is highly irritable and occasionally verbally abusive or threatening.	☐
6 Severe - Uncooperativeness and verbal abuse or threats notably influence the interview and seriously impact upon social relations. Patient may be violent and destructive but is not physically assaultive toward others.	☐
7 Extreme - Marked anger results in extreme uncooperativeness, precluding other interactions, or in episode(s) of physical assault toward others.	☐

NEGATIVE SCALE (N)

N1. Blunted affect Diminished emotional responsiveness as characterized by a reduction in facial expression, modulation of feelings, and communicative gestures. Basis for rating: observation of physical manifestations of affective tone and emotional responsiveness during the course of interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Changes in facial expression and communicative gestures seem to be stilted, forced, artificial, or lacking in modulation.	☐
4 Moderate - Reduced range of facial expression and few expressive gestures result in a dull appearance.	☐
5 Moderate severe - Affect is generally ~flat-, with only occasional changes in facial expression and a paucity of communicative gestures.	☐
6 Severe - Marked flatness and deficiency of emotions exhibited most of the time. There may be unmodulated extreme affective discharges, such as excitement, rage, or inappropriate uncontrolled laughter.	☐
7 Extreme - Changes in facial expression and evidence of communicative gestures are virtually absent. Patient seems constantly to show a barren or "wooden" expression.	☐

N2. Emotional withdrawal Lack of interest in, involvement with, and affective commitment to life's events. Basis for rating: reports of functioning from primary care workers or family and observation of interpersonal behavoir during the course of interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Usually lacks initiative and occasionally may show deficient interest in surrounding events.	☐
4 Moderate - Patient is generally distanced emotionally from the milieu and its challenges but, with encouragement, can be engaged.	☐
5 Moderate severe - Patient is clearly detached emotionally from persons and events in the milieu, resisting all efforts at engagement. Patient appears distant, docile, and purposeless but can be involved m communication at least briefly and tends to personal needs, sometimes with assistance.	☐
6 Severe - Marked deficiency of interest and emotional commitment results in limited conversation with others and frequent neglect of personal functions, for which the patient requires supervision	☐
7 Extreme - Patient is almost totally withdrawn, uncommunicative, a nd neglectful of personal needs as a result of profound lack of interest and emotional commitment.	☐

N3. Poor rapport Lack of interpersonal empathy, openess in conversation, and sense of closeness, interest, or involvement with the interviewer. This is evidenced by interpersonal distancing and reduced verbal and nonverbal communication. Basis for rating: interpersonal behavior during the course of interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Conversation is characterized by a stilted strained or artificial tone. It may lack emotional depth or tend to remain on an impersonal, intellectual plane.	☐
4 Moderate - Patient typically is aloof, with interpersonal distance quite evident. Patient may answer questions mechanically, act bored, or express disinterest.	☐
5 Moderate severe - Disinvolvement IS obvious and clearly impedes the productivity of the interview. Patient may tend to avoid eye or face contact.	☐
6 Severe - Patient is highly indifferent, with marked interpersonal distance. Answers are perfunctory, and there is little nonverbal evidence of involvement. Eye and face contact are frequently avoided.	☐
7 Extreme - Patient is totally uninvolved with the interviewer. Patient appears to be completely indifferent and consistently avoids verbal and nonverbal interactions during the interview.	☐

N4. Passive/apathetic social withdrawal Diminished interest and initiative in social interactions due to passivity, apathy, anergy, or avolition. This leads to reduced interpersonal involvement and neglect of activities of daily living. Basis for rating: reports on social behavior from primary care workers or family.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Shows occasional interest in social activities but poor initiative. Usally engages with others only when approached first by them.	☐
4 Moderate - Passively goes along with most social activities but in a disinterested or mechanical way. Tends to recede into the background.	☐
5 Moderate severe - Passively participates in only a minority of activities and shows virtually no interest or initiative Generally spends little time with others	☐
6 Severe - Tends to be apathetic and isolated, participating very rarely in social activities and occasionally neglecting personal needs. Has very few spontaneous social contacts.	☐
7 Extreme - Profoundly apathetic, socially isolated, and personally neglectful.	☐

N5. Difficulty in abstract thinking
Impairment in the use of the abstract-symbolic mode of thinking, as evidenced by difficulty in classification, forming generalizations, and proceeding beyond concrete or egocentric thinking in problemsolving tasks. Basis for rating: responses to questions on similarities and proverb interpretation, and use of concrete vs. abstract mode during the course of the interview.

1 **Absent** - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Tends to give literal or personalized interpretations to the more difficult proverbs and may have some problems with concepts that are fairly abstract or remotely related.	☐
4 Moderate - Often utilizes a concrete mode Has difficulty with most proverbs and some categories. Tends to be distracted by functional aspects and salient features	☐
5 Moderate severe - Deals primarily in a concrete mode, exhibiting difficulty with most proverbs and many categories.	☐
6 Severe - Unable to grasp the abstract meaning of any proverbs or figurative expressions and can formulate classifications for only the most simple of similarities. Thinking is either vacuous or locked into functional aspects, salient features, and idiosyncratic interpretations.	☐
7 Extreme - Can use only concrete modes of thinking. Shows no comprehension of proverbs, common metaphors or similes, and simple categories. Even salient and functional attributes do not serve as a basis for classification. This rating may apply to those who cannot interact even minimally with the examiner due to marked cognitive impairment.	☐

N6. Lack of spontaneity and flow of conversation
Reduction in the normal flow of communication associated with apathy, avolition, defensiveness, or cognitive deficit. This is manifested by diminished fluidity and productivity of the verbal-interactional process. Basis for rating: cognitive-verbal processes observed during the course of interview.

1 **Absent** - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Conversation shows little initiative. Patient's answers tend to be brief and unembellished, requiring direct and leading questions by the interviewer.	☐
4 Moderate - Conversation lacks free flow and appears uneven or halting. Leading questions are frequently needed to elicit adequate responses and proceed with conversation.	☐
5 Moderate severe - Patient shows a marked lack of spontaneity and openness, replying to the interviewer's questions with only one or two brief sentences.	☐
6 Severe - Patient's responses are limited mainly to a few words or short phrases intended to avoid or curtail communication. (E.g., "I don't know," "I'm not at liberty to say.") Conversation is seriously impaired as a result, and the interview is highly unproductive	☐
7 Extreme - Verbal output is restricted to, at most, an occasional utterance, making conversation not possible.	☐

N7. Stereotyped thinking Decreased fluidity, spontaneity, and flexibility of thinking, as evidenced in rigid, repetitious, or barren thought content. Basis for rating: cognitiveverbal processes observed during the interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Some rigidity shown in attitudes or beliefs. Patient may refuse to consider alternative positions or have difficulty in shifting from one idea to another.	☐
4 Moderate - Conversation revolves around a recurrent theme, resulting in difficulty in shifting to a new topic.	☐
5 Moderate severe - Thinking is rigid and repetitious to the point that despite the interviewer's efforts conversation is limited to only two or three dominating topics.	☐
6 Severe - Uncontrolled repetition of demands, statements, ideas, or questions which severely impairs conversation.	☐
7 Extreme - Thinking, behavior, and conversation are dominated by constant repetition of fixed ideas or limited phrases, leading to gross rigidity, inappropriateness, and restrictiveness of patient's communication.	☐

GENERAL PSYCHOPATHOLOGY SCALE (G)

G1. Somatic concern Physical complaints or beliefs about bodily illness or malfunctions. This may range from a vague sense of ill being to clear-cut delusions of catastrophic physical disease. Basis for rating: thought content expressed in the interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Distinctly concerned about health or somatic issues, as evidenced by occasional questions and desire for reassurance.	☐
4 Moderate - Complains about poor health or bodily malfunction, but there is no delusional conviction, and overconcern can be allayed by reassurance.	☐
5 Moderate severe - Patient expresses numerous or frequent complaints about physical illness or bodily malfunction, or else patient reveals one or two clearcut delusions involving these themes but is not preoccupied by them.	☐
6 Severe - Patient is preoccupied by one or a few clearcut delusions about physical disease or organic malfunction, but affect is not fully immersed in these themes, and thoughts can be diverted by the interviewer with some effort.	☐
7 Extreme - Numerous and frequently reported somatic delusions, or only a few somatic delusions of a catastrophic nature, which totally dominate the patient's affect and thinking.	☐

G2. Anxiety
Subjective experience of nervousness, worry, apprehension, or restlessness, ranging from excessive concern about the present or future to feelings of panic. Basis for rating: verbal report during the course of interview and corresponding physical manifestations.

1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Expresses some worry, overconcern, or subjective restlessness, but no somatic and behavioral consequences are reported or evidence.	☐
4 Moderate - Patient reports distinct symptoms of nervousness, which are reflected in mild physical manifestations such as fine hand tremor and excessive perspiration.	☐
5 Moderate severe - Patient reports serious problems of anxiety which have significant physical and behavioral consequences, such as marked tension, poor concentration, palpitations, or impaired sleep.	☐
6 Severe - Subjective state of almost constant fear associated with phobias, marked restlessness, or numerous somatic manifestations.	☐
7 Extreme - Patient's life is seriously disrupted by anxiety, which is present almost constantly and at times reaches panic proportion or is manifested in actual panic attacks.	☐

G3. Guiltfeelings
Sense of remorse or self-blame for real or imagined misdeeds in the past. Basis for rating: verbal report of guilt feelings during the course of interview and the influence on attitudes and thoughts.

1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Questioning elicits a vague sense of guilt or selfblame for a minor incident, but the patient clearly is not overly concerned	☐
4 Moderate - Patient expresses distinct concern over his responsibility for a real incident in his life but is not preoccupied with it, and attitude and behaviour are essentially unaffected.	☐
5 Moderate severe - Patient expresses a strong sense of guilt associated with self-deprication or the belief that he deserves punishment. The guilt feelings may have a delusional basis, may be volunteered spontaneously, may be a source of preoccupation and/or depressed mood, and cannot be allayed readily by the interviewer.	☐
6 Severe - Strong ideas of guilt take on a delusional quality and lead to an attitude of hopelessness or worthlessness The patient believes he should receive harsh sanctions for the misdeeds and may even regard his current life situation as such punishment.	☐
7 Extreme - Patient's life is dominated by unshakable delusions of guilt, for which he feels deserving of drastic punishment, such as life imprisonment, torture, or death. There may be associated suicidal thoughts or attribution of others' problems to one's own past misdeeds.	☐

G4. Tension
Overt physical manifestations of fear, anxiety, and agitation, such as stiffness, tremor, profuse sweating, and restlessness. Basis for rating: verbal report attesting to anxiety and, thereupon, the severity of physical manifestations of tension observed during the interview.

1 **Absent** - Definition does not apply	☐
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Posture and movements indicate slight apprehensiveness, such as minor rigidity, occasional restlessness, shifting of position, or fine rapid hand tremor.	☐
4 Moderate - A clearly nervous appearance emerges from various manifestations, such as fidgety behaviour, obvious hand tremor, excessive perspiration, or nervous mannerisms.	☐
5 Moderate severe - Pronounced tension is evidenced by numerous manifestations, such as nervous shaking, profuse sweating, and restlessness, but conduct in the interview is not significantly affected.	☐
6 Severe - Pronounced tension to the point that interpersonal interactions are disrupted. The patient for example, may be constantly fidgeting, unable to sit still for long, or show hyperventilation.	☐
7 Extreme - Marked tension is manifested by signs of panic or gross motor acceleration, such as rapid restless pacing and inability to remain seated for longer than a minute, which makes sustained conversation not possible	☐

G5. Mannerisms and posturing
Unnatural movements or posture as characterized by an awkward, stilted, disorganized, or bizarre appearance. Basis for rating: observation of physical manifestations during the course of interview as well as reports from primary care workers or family.

1 **Absent** - Definition does not apply	☐
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Slight awkardness in movements or minor rigidity of posture.	☐
4 Moderate - Movements are notably awkward or disjointed, or an unnatural posture is maintained for brief periods.	☐
5 Moderate severe - Occasional bizarre rituals or contorted posture are observed, or an abnormal position is sustained for extended periods.	☐
6 Severe - Frequent repetition of bizarre rituals, mannerisms, or stereotyped movements, or a contorted posture is sustained for extended periods..	☐
7 Extreme - Functioning is seriously impaired by virtually constant involvement in ritualistic, manneristic, or stereotyped movements or by an unnatural fixed posture which is sustained most of the time.	☐

G6. Depression Feelings of sadness, discouragement, helplessness, and pessimism. Basis for rating: verbal report of depressed mood during the course of interview and its observed influence on attitude and behavior.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Expresses some sadness or discouragement only on questioning. but there is no evidence of depression in general attitude or demeanor.	☐
4 Moderate - Distinct feelings of sadness or hopelessness, which may be spontaneously divulged, but depressed mood has no major impact on behavior or social functioning, and the patient usally can be cheered up.	☐
5 Moderate severe - Distinctly depressed mood is associated with obvious sadness, pessimism, loss of social interest psychomotor retardation, and some interference in appetite and sleep. The patient cannot be easily cheered up.	☐
6 Severe - Markedly depressed mood is associated with sustained feelings of misery, occasional crying, hopelessness, and worthlessness. In addition, there is major interference in appetite and/or sleep as well as in normal motor and social functions, with possible signs of self-neglect.	☐
7 Extreme - Depressive feelings seriously interfere in most major functions. The manifestations include frequent crying, pronounced somatic symptoms, impaired concentration, psychomotor retardation, social disinterest, self-neglect, possible depressive or nihilistic delusions, and/or possible suicidal thoughts or action.	☐

G7. Motor retardation Reduction in motor activity as reflected in slowing or lessening of movements and speech, diminished responsiveness to stimuli, and reduced body tone. Basis for rating: manifestations during the course of interview as well as reports by primary care workers or family.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Slight but noticeable diminution in rate of movements and speech Patient may be somewhat underproductive in conversation and gestures.	☐
4 Moderate - Patient is clearly slow in movements, and speech may be characterized by poor productivity, including long response latency, extended pauses, or slow pace.	☐
5 Moderate severe - A marked reduction in motor activity renders communication highly unproductive or delimits functioning in social and occupational situations. Patient can usually be found sitting or lying down.	☐
6 Severe - Movements are extremely slow, resulting in a minimum of activity and speech. Essentially the day is spent sitting idly or lying down.	☐
7 Extreme - Patient is almost completely immobile and virtually unresponsive to external stimuli.	☐

G8. Uncooperativeness Active refusal to comply with the will of significant others, including the interviewer, hospital staff, or family, which may be associated with distrust, defensiveness, stubbornness, negativism, rejection of authority, hostility, or belligerence. Basis for rating interpersonal behavior observed during the course of interview as well as reports by primary care workers or family.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Complies with an attitude of resentment, impatience, or sarcasm. May inoffensively object to sensitive probing during the interview.	☐
4 Moderate - Occasional outright refusal to comply with normal social demands, such as making own bed, attending scheduled programs, etc. The patient may project a hostile, defensive, or negative attitude but usually can be worked with.	☐
5 Moderate severe - Patient frequently ~s incompliant with the demands of his milieu and may be characterized by others as an "outcast" or having "a serious attitude problem." Uncooperativeness is reflected in obvious defensiveness or irritability with the interviewer and possible unwillingness to address many questions.	☐
6 Severe - Patient is highly uncooperative, negativistic, and possibly also belligerent. Refuses to comply with most social demands and may be unwilling to initiate or conclude the full interview.	☐
7 Extreme - Active resistance seriously impact on virtually all major areas of functioning. Patient may refuse to join in any social activities, tend to personal hygiene, converse with family or staff, and participate even briefly in an interview.	☐

G9. Unusual thought content Thinking characterized by strange, fantastic, or bizarre ideas, ranging from those which are remote or atypical to those which are distorted, illogical, and patently absurd. Basis for rating: thought content expressed during the course of interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Thought content is somewhat peculiar or idiosyncratic, or familiar ideas are framed in an odd context.	☐
4 Moderate - Ideas are frequently distorted and occasionally seem quite bizarre.	☐
5 Moderate severe - Patient expresses many strange and fantastic thoughts (e.g., being the adopted son of a king, being an escapee from death row) or some which are patently absurd (e.g., having hundreds of children, receiving radio messages from outer space through a tooth filling).	☐
6 Severe - Patient expresses many illogical or absurd ideas or some which have a distinctly bizarre quality (e.g., having three heads, being a visitor from another planet).	☐
7 Extreme - Thinking is replete with absurd, bizarre, and grotesque ideas.	☐

G10. Disorientation Lack of awareness of one's relationship to the milieu, including persons, place, and time, which may be due to confusion or withdrawal. Basis for rating: responses to interview questions on orientation.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - General orientation is adequate but there is some difficulty with specifics. For example, patient knows his location but not the street address, knows hospital staff names but not their functions, knows the month but confuses the day of week with an adjacent day, or errs in the date by more than two days. There may be narrowing of interest evidenced by familiarity with the immediate but not extended milieu such as ability to identify staff but not the Mayo;, Governor, or President.	☐
4 Moderate - Only partial success in recognizing persons, places, and time. For example, patient knows he is in a hospital but not its name, knows the name of his city but not the burrough or district, knows the name of his primary therapist but not many other direct care workers, knows the year and season but not sure of the month.	☐
5 Moderate severe - Considerable failure in recognizing persons, place, and time. Patient has only a vague notion of where he is and seems unfamiliar with most people in his milieu. He may identify the year correctly or nearly so but not know the current month, day of week, or even the season.	☐
6 Severe - Marked failure in recognizing persons, place, and time. For example, patient has no knowledge of his whereabouts, confuses the date by more than one year, can name only one or two individuals in his current life.	☐
7 Extreme - Patient appears completely disoriented with regard to persons, place, and time. There is gross confusion or total ignorance about one's location, the current year, and even the most familiar people, such as parents, spouse, friends, and primary therapist.	☐

G11. Poor attention Failure in focused alertness manifested by poor concentration, distractibility from internal and external stimuli, and difficulty in harnessing, sustaining, or shifting focus to new stimuli. Basis for rating: manifestations during the course of interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Limited concentration evidenced by occasional vulnerability, to distraction or faltering attention toward the end of the interview.	☐
4 Moderate - Conversation is affected by the tendency to be easily distracted, difficulty in long sustaining concentration on a given topic, or problems in shifting attention to new topics.	☐
5 Moderate severe - Conversation is seriously hampered by poor concentration, distractibility, and difficulty in shifting focus appropriately.	☐
6 Severe - Patient's attention can be harnessed for only brief moments or with great effort, due to marked distraction by internal or external stimuli.	☐
7 Extreme - Attention is so disrupted that even brief conversation is not possible.	☐

G12. Lack of judgment and insight Impaired awareness or understanding of one's own psychiatric condition and life situation. This is evidenced by failure to recognize past or present psychiatric illness or symptoms, denial of need for psychiatric hospitalization or treatment, decisions characterized by poor anticipation of consequences, and unrealistic short term and long-range planning. Basis for rating: thought content expressed during the interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Recognizes having a psychiatric disorder but clearly underestimates its seriousness, the implications for treatment, or the importance of taking measures to avoid relapse. Future planning may be poorly conceived.	☐
4 Moderate - Patient shows only a vague or shallow recognition of illness. There may be fluctuations in acknowledgement of being ill or little awareness of major symptoms which are present, such as delusions, disorganized thinking, suspiciousness, and social withdrawal. The patient may rationalize the need for treatment in terms of its relieving lesser symptoms, such as anxiety, tension, and sleep difficulty.	☐
5 Moderate severe - Acknowledges past but not present psychiatric disorder. If challenged, the patient may concede the presence of some unrelated or insignificant symptoms, which tend to be explained away by gross misinterpretation or delusional thinking. The need for psychiatric treatment similarly goes unrecognized.	☐
6 Severe - Patient denies ever having had a psychiatric disorder. He disavows the p resence of any psychiatric symptoms in the past or present and, though compliant, denies the need for treatment and hospitalization.	☐
7 Extreme - Emphatic denial of past and present psychiatric illness. Current hospitalization and treatment are given a delusional interpretation (e.g., as punishment for misdeeds, as persecution by tormentors, etc.), and the patient may thus refuse to cooperate with therapists, medication, or other aspects of treatment.	☐

G13. Disturbance of volition Disturbance in the wilful initiation, sustenance, and control of one's thoughts, behavior, movements, and speech. Basis for rating thought content and behavior manifested in the course of interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - There is evidence of some indecisiveness in conversation and thinking, which may impede verbal and cognitive processes to a minor extent.	☐
4 Moderate - Patient is often ambivalent and shows clear difficulty in reaching decisions. Conversation may be marred by alternation in thinking, and in consequence verbal and cognitive functioning are clearly impaired.	☐
5 Moderate severe - Disturbance of volition interferes in thinking as well as behavior. Patient shows pronounced indecision that impedes the initiation and continuation of social and motor activities, and which also may be evidenced in halting speech.	☐
6 Severe - Disturbance of volition interferes in the execution of simple, automatic motor functions, such as dressing and grooming, and markedly affects speech.	☐
7 Extreme - almost complete failure of volition is manifested by gross inhibition of movement and speech, resulting in immobility and/or mutism.	☐

G14. Poor impulse control

Disordered regulation and control of action on inner urges resulting in sudden, unmodulated, arbitrary, o; misdirected discharge of tension and emotions without concern about consequences. Basis for rating: behavior during the course of interview and reported by primary care workers or family.

1 **Absent** - Definition does not apply	☐
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 **Mild** - Patient tends to be easily angered and frustrated when facing stress or denied gratification but rarely acts on impulse.	☐
4 **Moderate** - Patient gets angered and verbally abusive with minimal provocation. May be occasionally threatening, destructive, or have one or two episodes involving physical confrontation or a minor brawl.	☐
5 **Moderate severe** - Patient exhibits repeated impulsive episodes involving verbal abuse destruction of property, or physical threats. There may be one or two episodes involving serious assault, for which the patient requires isolation, physical restraint, or p.r n. sedation.	☐
6 **Severe** - Patient frequently is impulsively aggressive, threatening, demanding, and destructive, without any apparent consideration of consequences. Shows assaultive behavior and may also be sexually offensive and possibly respond behaviorally to hallucinatory commands.	☐
7 **Extreme** - Patient exhibits homicidal attacks, sexual assaults, repeated brutality, or self-destructive behavior. Requires constant direct supervision or external constraints because of inability to control dangerous impulses.	☐

G15. Preoccupation

Absorption with internally generated thoughts and feelings and with autistic experiences to the detriment of reality orientation and adaptive behavior. Basis for rating: interpersonal behavior observed during the course of interview.

1 **Absent** - Definition does not apply	☐
2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 **Mild** - Excessive involvement with personal needs or problems, such that conversation veers back to egocentric themes and there is diminished concern exhibited toward others.	☐
4 **Moderate** - Patient occasionally appears selfabsorbed, as if daydreaming or involved with internal experiences, which interferes with communication to minor extent.	☐
5 **Moderate severe** - Patient often appears to be engaged in autistic experiences, as evidenced by behaviors that significantly intrude on social and communicational functions, such as the presence of a vacant stare, muttering or talking to oneself, or involvement with stereotyped motor patterns.	☐
6 **Severe** - Marked preoccupation with autistic experiences, which seriously delimits concentration, ability to converse, and orientation to the milieu. The patient frequently may be observed smiling, laughing, muttering, talking, or shouting to himself.	☐
7 **Extreme** - Gross absorption with autistic experiences, which profoundly affects all major realms of behavior. The patient constantly may be responding verbally and behaviorally to hallucinations and show little awareness of other people or the external milieu.	☐

G16. Active social avoidance Diminished social involvement associated with unwarranted fear, hostility, or distrust. Basis for rating: reports of social functioning by primary care workers or family.	
1 **Absent** - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Patient seems ill at ease in the presence of others and prefers to spend time alone, although he participates in social functions when required.	☐
4 Moderate - Patient begrudgingly attends all or most social activities but may need to be persuaded or may terminate prematurely on account of anxiety, suspiciousness, or hostility.	☐
5 Moderate severe - Patient fearfully or angrily keeps away from many social interactions despite others' efforts to engage him. Tends to spend unstructured time alone.	☐
6 Severe - Patient participates in very few social activities because of fear, hostility, or distrust. When approached, the patient shows a strong tendency to break off interactions, and generally he tends to isolate himself from others.	☐
7 Extreme - Patient cannot be engaged in social activities because of pronounced fears, hostility, or persecutory delusions. To the extent possible, he avoids all interactions and remains isolated from others.	☐

ANNEXURE VII

MONTGOMERY-ASBERG DEPRESSION RATING SCA

Montgomery-Asberg Depression Rating Scale (MADRS)

DATE: **TOTAL SCORE:**

1. Apparent sadness

Representing despondency, gloom and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

0 = No sadness.
2= Looks dispirited but does brighten up without difficulty.
4= Appears sad and unhappy most of the time.
6= Looks miserable all the time. Extremely despondent

2. Reported sadness

Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope.

0 = Occasional sadness in keeping with the circumstances.
2 = Sad or low but brightens up without difficulty.
4 = Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
6 = Continuous or unvarying sadness, misery or despondency.

3. Inner tension

Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.

0= Placid. Only fleeting inner tension.
2= Occasional feelings of edginess and ill-defined discomfort.
4= Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
6 = Unrelenting dread or anguish. Overwhelming panic.

4. Reduced sleep

Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.

0 = Sleeps as normal.
2 = Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
4 = Moderate stiffness and resistance
6 = Sleep reduced or broken by at least 2 hours.

5. Reduced appetite

Representing the feeling of a loss of appetite compared with when-well. Rate by loss of desire for food or the need to force oneself to eat.

0 = Normal or increased appetite.

2 = Slightly reduced appetite.
4 = No appetite. Food is tasteless.
6 = Needs persuasion to eat at all.

6. Concentration difficulties

Representing difficulties in collecting one's thoughts amounting to an incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.
0 = No difficulties in concentrating.
2 = Occasional difficulties in collecting one's thoughts.
4 = Difficulties in concentrating and sustaining thought which reduced ability to read or hold a conversation.
6 = Unable to read or converse without great difficulty.

7. Lassitude

Representing difficulty in getting started or slowness in initiating and performing everyday activities.
0 = Hardly any difficulty in getting started. No sluggishness.
2 = Difficulties in starting activities.
4 = Difficulties in starting simple routine activities which are carried out with effort.
6 = Complete lassitude. Unable to do anything without help.

8. Inability to feel

Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.
0 = Normal interest in the surroundings and in other people.
2 = Reduced ability to enjoy usual interests.
4 = Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
6 = The experience of being emotionally paralysed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9. Pessimistic thoughts

Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.
0 = No pessimistic thoughts.
2 = Fluctuating ideas of failure, self-reproach or self- depreciation.
4 = Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
6 = Delusions of ruin, remorse or irredeemable sin. Self- accusations which are absurd and unshakable.

10. Suicidal thoughts

Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicide attempts should not in themselves influence the rating.
0 = Enjoys life or takes it as it comes.
2 = Weary of life. Only fleeting suicidal thoughts.
4 = Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
6 = Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

ANNEXURE VIII

NARANJOS SCALE

ADVERSE DRUG REACTION ASSESSMENT SCALE

Suspected drug:
Description of reaction:

Are there previous conclusive reports on this reaction	Yes=1 No=0 Don't know or not done=0	
Did the adverse events appear after the suspected drug was given?	Yes=2 No=-1 Don't know or not done=0	
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	Yes=1 No=0 Don't know or not done=0	
Did the adverse reaction appear when the drug was administered?	Yes=2 No=-1 Don't know or not done=0	
Are there alternative causes that could have caused the reaction?	Yes=-1 No=2 Don't know or not done=0	
Did the reaction reappear when the placebo was given?	Yes=-1 No=1 Don't know or not done=0	
Was the drug detected in any body fluid in toxic concentrations?	Yes=1 No=0 Don't know or not done=0	
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	Yes=1 No=0 Don't know or not done=0	
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	Yes=1 No=0 Don't know or not done=0	
Was the adverse event confirmed by any objective evidence?	Yes=1 No=0 Don't know or not done=0	
Total Score		

Scoring

≥9= definite ADR
5-8= Probable ADR
1-4= Possible ADR
0= doubtful ADR

Name of the pharmacist : ..... Sign : .....

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Place : DHARMAPURI

Date: **SHAYANA.S**

LIST OF ABBREVIATIONS

1.	ADR	Adverse Drug Reaction
2.	CBT	Cognitive Behavioral Therapy
3.	CT	Computerized Tomography
4.	DBS	Deep Brain Stimulation
5.	DM	Diabetes Mellitus
6.	ECT	Electro Convulsive Therapy
7.	EPS	Extra Pyramidal Symptoms
8.	FGA	First Generation Antipsychotics
9.	GI	Gastrointestinal
10.	HAM-D	Hamilton Depression
11.	IDS-C	Inventory Of Depressive Symptomatology- Clinician rated
12.	IRT	Item Response Theory
13.	MRI	Magnetic Resonance Imaging
14.	RDC	Montgomery-Asberg Depression Rating Scale
15.	PANSS	Positive And Negative Syndrome Scale
16.	rTMS	Repeated Transcranial Magnetic Stimulation
17.	RDC	Research Diagnostic Criteria
18.	SGA	Second Generation Antipsychotics
19.	SSRI	Selective Serotonin Reuptake Inhibitor
20.	SD	Standard Deviation
21.	tDCS	Transcranial Direct Current Stimulation
22.	TRD	Treatment Resistant Depression

23.	TRS	Treatment Resistant Schizophrenia
24.	TCA	Tricyclic Antidepressants
25.	VNS	Vagal Nerve Stimulation
26.	WHO	World Health Organization